25 July 2024
EMA/378968/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyloy

International non-proprietary name: zolbetuximab

Procedure No. EMEA/H/C/005868/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine 3
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
CAPOX	capecitabine and oxaliplatin
CHO	Chinese Hamster Ovary
CI	confidence interval
CLDN	claudin
CLDN18.1	claudin-18 splice variant 1
CLDN18.2	claudin-18 splice variant 2
CPP	critical process parameters
CPS	combined positive score
CQA	critical quality attributes
CT	chemotherapy
CTM	clinical trial material
DCR	disease control rate
DoE	design of Experiment
DOR	duration of response
dQTcF	baseline-adjusted QT interval corrected for heart rate according to Fridericia's formula
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
EOX	epirubicin, oxaliplatin and capecitabine
FAS	full analysis set
GC	gastric cancer
GEJ	gastroesophageal junction
GHS/QoL	Global Health Status/Quality of Life
GMP	Good Manufacturing Practice
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IgG1	immunoglobulin G subclass 1
IHC	immunohistochemistry
IRC	independent review committee
IRR	infusion-related reaction
ISS	integrated summary of safety
iv	intravenous

mFOLFOX6	modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin
MMRd	mismatch repair deficiency
MoA	mode of action
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NE	not estimable
NK-1	neurokinin 1
OG25-Pain	Oesophago-Gastric Questionnaire on Abdominal Pain and Discomfort
ORR	objective response rate
OS	overall survival
PARs	Proven Acceptable Ranges
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand 1
PF	physical function
PFS	progression-free survival
PR	partial response
PT	preferred term
Q2W	every 2 weeks
Q2WBSA	every 2 weeks dosing for the BSA-normalized regimen
Q3W	every 3 weeks
Q3WBSA	every 3 weeks dosing for the BSA-normalized regimen
QLQ-C30	Quality of Life Questionnaire - Core Questionnaire
QLQ-OG25	Quality of Life Questionnaire - Oesophago-Gastric Module
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia’s formula
SAE	Serious Adverse Event
SAF	safety analysis set
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
TTCD	time to confirmed deterioration
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 21 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Vyloy, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 February 2021.

Vyloy, was designated as an orphan medicinal product EMA/OD/083/10 on 26/11/2010 in the following condition: treatment of locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Vyloy as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Vyloy.

The applicant applied for the following indication: Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0090/2020 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance zolbetuximab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
12 October 2017	EMEA/H/SA/3652/1/2017/III	Dr Serena Marchetti, Dr Sheila Killalea and Dr Jan Mueller-Berghaus
31 May 2018	EMEA/H/SA/3652/2/2018/PA/II	Dr Pierre Demolis and Dr Paolo Foggi
26 July 2018	EMEA/H/SA/3652/3/2018/PA/II	Ms Blanca García-Ochoa Martín and Dr Serena Marchetti
31 January 2019	EMEA/H/SA/3652/4/2018/PA/I	Dr Stephan Lehr and Dr Jens Reinhardt
25 June 2020	EMEA/H/SA/3652/4/FU/1/2020/PA/I	Dr Stephan Lehr and Dr Jens Reinhardt

The Protocol assistance/Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the proposed comparability plan for different drug substance batches; agreement to a proposed commercial manufacturing site; acceptability of setting shelf life for drug substance acceptability of the proposed drug product process validation plan and additional presentation can be approved.

- Acceptability of the overall clinical pharmacology plan. Acceptability of the study design for study 8951-CL-0301, in particular the selected patient population, the backbone combination chemotherapy regimen, primary and key secondary efficacy endpoints,

- Agreement with the study design of Study 8951-CL-0302 in particular the selected patient population, the backbone combination chemotherapy regimen, primary and key secondary efficacy endpoints and the statistical analysis.

- Agreement with a randomized study design with a safety lead-in period for Study 8951-CL-5201, the choice of the chemotherapy backbone, study population and proposed diagnostic test, proposed primary endpoint and key secondary endpoints as well statistical plan.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Carolina Prieto Fernandez

The application was received by the EMA on	21 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	2 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 January 2024
A pre-approval GMP inspection at the site intended for the Drug Substance manufacturing activities was carried out in June 2024. The outcome of the inspection carried out was provided on 22 July 2024.	22 July 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 February 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 July 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vyloy on	25 July 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 July 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially claimed therapeutic indication was:

"*Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 5.1).*"

2.1.2. Epidemiology and screening tools/prevention

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer death worldwide [Morgan et al, 2022; Sung et al, 2021]. In 2020, there were an estimated 1.1 million new cases and approximately 770 000 deaths worldwide from gastric cancer. Incidence and mortality of gastric cancer is about 2-fold higher in males vs females. Eastern Asia (primarily China) comprises about 60% of the global cases of gastric cancer.

The incidence and mortality of gastric cancer are generally directly correlated, with the notable exception of Japan and Korea, which have a high 5-year survival rate (> 60%) due to the implementation of population-based screening and awareness programs that detect more cancers at an early stage [Morgan et al, 2022; GBD 2017 Stomach Cancer Collaborators, 2020; Matsuda & Saika, 2018].

In Europe, the overall 5-year survival rate of gastric cancer for all stages of gastric cancer combined was estimated at 26% [Rawla & Barsouk, 2019], in China about 35% [Zeng et al, 2018; Allemani et al, 2018] and in the US 43% [Li et al, 2022].

2.1.3. Biologic features

HER2 (human epidermal growth factor receptor 2) is overexpressed for approximately 20% of patients with locally advanced or metastatic gastric/GEJ adenocarcinoma.

CLDN18.2 is a member of the CLDN family of more than 20 structurally related proteins that are involved in the formation of tight junctions in epithelia and endothelia *[Niimi et al, 2001]*. Tight junctions are essential for the tight sealing of the cellular sheets forming a luminal barrier and controlling paracellular ion flux. There are 2 main splice variants of CLDN18, one of which is mainly expressed in the lung (CLDN18.1) and the other is predominantly expressed in the stomach (CLDN18.2).

CLDN18.2 is a highly cell type-specific differentiation antigen that is expressed by differentiated gastric mucosa cells in the pit and base regions of gastric glands. Moreover, CLDN18.2 is not detectable in any other normal cell type of the human body either at transcript level or as protein. CLDN18.2 is expressed in a number of human cancers including gastric and pancreatic adenocarcinomas *[Lee et al, 2011]*. The expression of CLDN18.2 is retained upon malignant transformation of gastric epithelia and is present in approximately 80% of primary gastric adenocarcinomas. CLDN18.2 expression was detected in diffuse and intestinal gastric adenocarcinomas *[Sahin et al, 2008]*. CLDN18.2 is also expressed in lymph node metastases of gastric adenocarcinomas and in distant metastases, including bile duct, lung, and the ovary (Krukenberg tumors).

In a recent study evaluating the association of CLDN18 protein expression with clinicopathological features and prognosis in a series of 350 advanced gastric and GEJ adenocarcinomas, similar overlap of other therapeutic biomarkers (HER2, PD-L1 [CPS $\geq$ 1 and CPS $\geq$ 5] and MMRd) was found in CLDN18.2 positive and negative tumors, suggesting that the expression of these biomarkers and CLDN18.2 are not interdependent. In addition, CLDN18 expression was not correlated with OS in gastric or GEJ cancer in this study *[Pellino et al, 2021]*, a finding that was also confirmed in another study *[Kubota et al, 2023]*.

2.1.4. Clinical presentation, diagnosis

Most patients have symptoms of advanced stage gastric cancer at the time they are diagnosed. In patients with metastatic disease, survival rates are markedly lower with an estimated 5-year survival rate of 6%. Globally, expected median survival for unresectable advanced or metastatic HER2-negative gastric/GEJ cancer with currently available standard of care is just under 1 year based on "all comers" data from the CheckMate 649 study *[Janjigian et al, 2021b; Sun & Yan, 2016]*. There remains a serious unmet medical need for the treatment of locally advanced unresectable or metastatic gastric and GEJ adenocarcinoma.

2.1.5. Management

Currently recommended first-line therapies for locally advanced unresectable or metastatic disease include chemotherapy backbone (fluoropyrimidine- and platinum-containing cytotoxic drugs) in combination with therapy depending on HER2 and PD-L1 CPS status [Ajani et al, 2022; Lordick et al, 2022]:

- For HER2 overexpressing cancer, the treatment option is chemotherapy in combination with trastuzumab. KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy was approved in August 2023 (Keytruda II/133) for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS $\geq$ 1.
- For the 80% of patients with HER2-negative locally advanced or metastatic gastric/GEJ adenocarcinoma, the treatment is chemotherapy alone or, based on PD-L1 CPS status, in combination with nivolumab or pembrolizumab. OPDIVO was approved in 2021 (Opdivo II/96) in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) $\geq$ 5. Keytruda received an approval in November 2023 (Keytruda II/135) for the first-line treatment of HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS $\geq$ 1.

2.2. About the product

Zolbetuximab (formerly known as IMAB362) is a chimeric (mouse/human) IgG1 antibody directed against the tight junction molecule CLDN18.2. CLDN18.2 is a highly tissue specific cell surface molecule that is expressed in normal gastric tissue as well as in many human cancers (please see 2.1.3). Zolbetuximab was generated by recombinant DNA technology and gene synthesis by joining mouse variable regions obtained from a CLDN18.2-specific murine hybridoma clone to human antibody kappa light and IgG1 heavy chain constant regions.

Antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are the identified modes of action (MoAs) mediated by the Fc region of zolbetuximab.

The claimed indication of zolbetuximab is in combination with chemotherapy for advanced or metastatic HER2-negative, CLDN18.2-positive gastric or GEJ adenocarcinoma.

The final approved indication is:

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative

gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 4.2 of the SmPC).

The recommended Vyloy dosage is 800 mg/m² IV Cycle 1, Day 1 as a single loading dose, followed by maintenance doses of 600 mg/m^2 intravenously every 3 weeks or 400 mg/m2 intravenously every 2 weeks.

2.3. Type of application and aspects on development

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as powder for concentrate for solution for infusion containing 100 mg of zolbetuximab as active substance (AS). After reconstitution, each mL of solution contains 20 mg of zolbetuximab.

Other ingredients are: arginine, phosphoric acid (E 338), sucrose, and polysorbate 80 (E 433).

The product is available in 20 mL Type I glass vial with European blow-back feature, grey bromobutyl rubber stopper with ethylene tetrafluoroethylene film, and aluminium seal with a green cap.

2.4.2. Active substance

2.4.2.1. General information

The active substance (*INN z*olbetuximab) is a chimeric (mouse/human) IgG1 antibody produced in Chinese Hamster Ovary (CHO) cells by standard recombinant expression technology. Zolbetuximab is directed against the tight junction protein, claudin-18 splice variant 2 (CLDN18.2), a transmembrane protein that in healthy tissue is expressed exclusively on gastric epithelial cells in the pit and base regions of the gastric glands. CLDN18.2 is expressed in primary gastric, oesophageal and pancreatic adenocarcinomas and is maintained in the course of malignant transformation. As modes of action (MoAs), Zolbetuximab mediates an efficient lysis of CLDN18.2-positive cells through antibody dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

2.4.2.2. Manufacture, process controls and characterisation

Manufacture

Description of the manufacturing process

Zolbetuximab active substance is manufactured at Patheon Biologics LLC, 4766 LaGuardia Drive, Saint Louis, Missouri 63134-3116 United States (Patheon). During the assessment, a Major Objection (MO) was raised, requesting confirmation by means of an on-site GMP re-inspection that the Patheon site is considered GMP compliant to perform the manufacturing activities intended for Vyloy. A GMP inspection

was conducted and confirmation was received that the site can be considered GMP compliant. The MO was considered solved.

All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

Process flow diagrams of the cell culture and purification processes are presented.

Zolbetuximab AS is manufactured using the CHO cell line in a fed batch process. A subculture is initiated by thawing and inoculating cells from one vial of working cell bank (WCB) into cell growth medium, and cells are expanding in increasing culture volumes. Thawing conditions for the WCB vial used for the manufacture of the AS are described. The production culture step is identified as critical for the control of critical quality attributes (CQAs).

The cell culture fluid is subsequently purified through a series of chromatographic and filtration steps.

The validated hold times are indicated and a tabular overview about the maximum hold times at each stage together with an appropriate justification was provided. Reprocessing is allowed in two cases, which is adequately reflected in the dossier.

Control of material

Compendial and non-compendial raw materials are listed together with adequate specifications. Media and buffer composition is provided too. No human or animal derived materials are used in the active substance manufacturing process other than the production cell line of Chinese hamster ovary origin. Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. To generate the antibody by mouse hybridoma technology, mice were immunized. After immunization, the splenocytes were isolated and fused with myeloma cells to generate hybridoma cell lines. Candidate hybridoma cell lines were screened by flow cytometry for the presence of CLDN18.2 binding antibodies. The CLDN18.2 specific antibody produced by the hybridoma was chimerized. The DNA sequences encoding heavy chain and light chain were codon optimized. The fragments were inserted into CHO expression vectors. The Applicant described sufficiently detailed the process of construction of the optimized heavy and light chains constituting zolbetuximab. A clonal CHO cell line suitable for the manufacture of the AS was constructed, evaluated and selected. Safety testing of the MCB was performed in accordance with ICH Q5A and confirmed absence of mycoplasma and viruses. The quality of zolbetuximab AS derived from of MCB was confirmed to be comparable to the reference standard. The Applicant provided a short description of the generation of the first production cell line.

WCBs were tested for absence of adventitious agents. Reduced testing of the WCB and absence of in vivo testing is considered acceptable. New WCBs will be evaluated for safety and identified cell line species in accordance with ICH guidelines. The tests and acceptance criteria applied for the safety and identity of new WCBs will be the same criteria as those used to establish the safety and cell line identity of the current WCB. Characterization and safety testing and genetic stability study of EOPC-LIVCA and MCB were performed and the results demonstrated that the production cell line of the AS was stable through MCB to EOPC-LIVCA. The labelling/documentation system for the MCB/WCB, ensuring the proper and permanent identification of the vials constituting the banks is described by the Applicant.

Control of critical steps

Steps with critical process parameters (CPPs) and/or critical In-Process Controls (IPCs) are defined as critical steps. CPPs are already indicated in the manufacturing description. The classification and the respective justification are provided and found acceptable.

Process validation

The commercial manufacturing process (Process D) was qualified with process performance qualification (PPQ) batches. These PPQ batches were executed under process validation (PV) protocols at commercial scale in the commercial manufacturing facility to demonstrate process consistency in commercial manufacturing. In addition to the execution of PPQ batches, several validation studies were concurrently conducted. Stage 3 of the PV process is termed continued process verification by which Process D will be verified continuously through a continued process verification (CPV) program.

PPQ batches were executed at commercial scale in the commercial manufacturing facility to demonstrate process consistency in commercial manufacturing. The PPQ batches were operated within Normal Operating Ranges (NORs) and met pre-determined criteria for process indicators and IPCs. The results of all process parameters and IPCs demonstrate that the process met the criteria for process performance and product quality. Thus, the process can be considered validated.

The clearance of process-related impurities has been monitored and data indicate sufficient clearance of all potential impurities; the safety evaluation is discussed in the dossier. *Process Characterisation*

In-process pool hold times have been established.

Resin lifetime validation studies were also performed to evaluate whether resins maintain their intended functions for a pre-determined number of cycles. Regarding shipping qualification, the results of these studies guaranteed that the proposed shipper can maintain the product temperature conditions.

Manufacturing process development

In order to identify process parameters which could potentially impact on critical quality attributes (CQAs) and performance indicators (PIs), process risk assessment was conducted based on prior knowledge which includes experiences from the process development of AS and its similar products of monoclonal antibodies. The criticality classification of quality attributes for AS for the low, medium, high, and obligatory attributes is provided. This is considered sufficient.

The AS and FP process risks were determined based on the extent of process understanding for each CQA. Such process understanding was obtained from prior knowledge and a series of process characterization studies. Process characterization studies were conducted using scale-down models (SDMs) which were demonstrated to be representative and appropriate for predicting responses of the commercial-scale unit operations. A process risk assessment was performed. The applicant refers to the determination of criticalities and Proven Acceptable Ranges (PARs) of process parameters procedure, which is acknowledged.

With regard to leachables and extractables a risk assessment is provided. Based on the risk assessment and a product specific leachable study it is concluded that the amount of leachable material in AS is expected to be well within the acceptable limits.

Four manufacturing processes have been established for zolbetuximab active substance referred to as Process A to D. Process D derived material is considered representative for the commercial process, e.g. for stability. As material from Process A to C was used in clinical trials, sufficient comparability between these materials is essential to draw relevant conclusion from clinical data and comparability of these materials to Process D derived material is a pre-requisite for commercialisation. The first GMP batch manufactured with the initial Process A was already used in clinical trials. Overall sufficient comparability of materials manufactured with initial Process A and optimized Process A can be concluded. Analytical comparability study was to assess the comparability of AS manufactured by Process A and Process B. The assessment also evaluated the comparability of AS manufactured by Process B at different scales. The number of batches used in comparability exercises is considered sparse. Results are provided and confirm the Process A and Process B comparability as well as comparability between Process B and

Process C derived materials. The totality of data allows the conclusion that AS manufactured by Process C can be considered sufficiently comparable with that manufactured by Process B to rely on clinical data obtained with Process B and C derived material. The results of the comparability exercise demonstrate that Process C and Process D batches can be considered comparable regarding the physicochemical and biological product characteristics and the degradation pathways.

Characterisation

Elucidation of structure and other characteristics

Zolbetuximab is a recombinant chimeric (mouse/human) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by standard recombinant expression technology. The antibody is directed against claudin-18 splice variant 2 (CLDN18.2). Zolbetuximab is a heterogenous mixture of related species.

Zolbetuximab contains a single N-glycosylation site at Asn298 on each heavy chain based on the presence of a consensus sequence. Reduced peptide mapping analysis experimentally confirmed that each heavy chain is glycosylated with the predicted glycoform. .Multiple analytical methodologies were used for analysis of glycan composition. The biological effects of deglycosylated species, galactosylated species and fucosylated species were investigated. Zolbetuximab binds to CLDN18.2 on the surface of target tumor cells and shows anti-tumor activity via ADCC and CDC activity by host immune system triggered by the monoclonal antibody Fc region. Specific binding of zolbetuximab to CLDN18.2 was evaluated.

Size variants of zolbetuximab AS were assessed. Charged variants were further fractionated and characterized.

Impurities

Process-related impurities are identified for zolbetuximab AS. Purification process effectively removes these impurities and risk assessments were provided based on Permitted Daily Exposure (PDE). The handling of process-related impurities (process characterisation, validation, risk assessment and control strategy) is acceptable. Relevant product–related impurities are covered by the implemented control strategy.

2.4.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Control of active substance

Specifications are set in accordance with ICH Q6B. All relevant characteristics of zolbetuximab AS (identity, content, potency, purity, impurities and safety) are adequately covered.

The specification for AS has been updated during development to reflect better understanding of the process and the product. Some methods were removed from the specification or moved to in-process testing based on deep understanding of quality attributes and process control. Other methods were replaced with more robust ones but bridging studies support the results obtained with these methods.

Specifications to control process related impurities were included.

Batch analysis

Batch analysis of the AS manufactured by Process A, B, C and D were provided.

The results are within the specifications and confirm consistency of the manufacturing process.

Reference standards or materials

A two-tiered reference standard system is established consisting of the primary and working reference standard representing the same material derived from AS batch manufactured with the commercial process D. Release testing results (qualification of the material) were provided. Future reference standards will be established as deemed necessary and qualified according to an established test program.

Container closure system

The container closure system of zolbetuximab active substance is listed and found adequate. With regard to leachables and extractables, a risk assessment was provided. Based on the risk assessment (including data from vendors) and a product specific leachable study it is concluded that for all process contact materials, including the final container closure system, the amount of leachable material in AS is expected to be well within the acceptable limits. Information regarding the supplier of the AS container-closure material is provided.

2.4.2.4. Stability

The primary and supportive stability studies of AS manufactured at Patheon are carried out using AS manufactured with Process D which reflect commercial production. The stability studies are performed at -70 ± 10°C for long term storage condition up to 60 months, 5 ± 3°C for accelerated storage condition and 25 ± 2°C /60 ± 5% RH for stressed condition. The stability protocol lasting 60 months at the intended long-term conditions of -70 ± 10°C is provided by the Applicant, of which currently 48 months of real time data are available for both the primary stability and supportive batches to support the shelf-life claim for the AS is detailed.

In conclusion, the information is adequate and supports the shelf-life claim of 48 months for the AS, under the proposed storage conditions.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

Zolbetuximab finished product is a sterile, preservative-free, white to off-white lyophilized powder, supplied in a single-dose vial. The FP is reconstituted with sterile water for injection (WFI). The volume of WFI for reconstitution is 5.0 mL. The composition of reconstituted FP is 20 mg/mL zolbetuximab, arginine, sucrose, polysorbate 80 and phosphoric acid.

The impact of the formulation parameters on zolbetuximab stability in the lyophilized product was examined using the Design of Experiments (DoE)-based approach. Results of the study indicate suitability of the formulation parameters on FP stability.

The FP manufacturing process used in clinical studies was developed (Process A). An initial manufacturing process for 22 mg/vial was followed by development of 105 mg/vial which resulted in vial containing five times higher extractable amount of zolbetuximab. Process A has subsequently been modified to establish the process at the intended commercial site and scale (Process B). An initial process of clinical trial material (CTM) was developed.

It is noticed that the long-term storage conditions for Process A, 105 mg/vial (-20 ± 5°C) are different than the long-term conditions for Process B, 105 mg/vial (5 ± 3°C). The manufacturing processes include AS thawing, compounding, sterile filtration, aseptic filling, lyophilization, capping and visual inspection. There were no formulation changes during clinical development since Phase 1 clinical studies.

Overall, the changes to the process (site change, scale-up and minor adaptions of the process parameters) are not considered to have a major impact on FP quality. The totality of data (release, extended characterisation and stability) indicate that zolbetuximab FP manufactured with FP Process B can be considered sufficiently comparable to FP manufactured with FP Process A.

The primary packaging components, Type I glass vial and stopper, meet U.S. Pharmacopeia and European Pharmacopoeia compendial requirements for glass containers for pharmaceutical use and elastomeric closures for injection. With regard to leachables/extractables, the applicant refers to the nature of the FP which is a lyophilized product and it is unlikely that the FP comes into contact with the stopper during shelf life; there is no solvent in the FP to facilitate leachables. The risk of leachables from the glass vial into the FP was considered low because it is solid-solid phase interaction and the reconstituted FP is only in transient contact with the container closure. Therefore, the risk of leachables from the glass vial and stopper for reconstituted FP was considered low, which is acknowledged.

Numerous compatibility studies were conducted and for all materials/conditions investigated, there were no significant change in quality attributes for all samples including reconstituted FP and infusion solution. This indicated that reconstituted zolbetuximab FP and solution for infusion are compatible with most commonly used infusion equipment(s). Adequate results of microbial challenge studies have been provided.

2.4.3.2. Manufacture of the product and process controls

Description of manufacturing process and process control

All sites involved in manufacture and quality control (QC) testing of the finished product operate in accordance with EU GMP.
Astellas Ireland Co. Limited, Killorglin Co. Kerry, V93 FC86, Ireland is the authorised EU batch release site.

A flow diagram for the Manufacturing Process of Finished Product is provided. The finished product manufacture is a straightforward thawing, compounding, filtration and aseptic filling process which has been described in sufficient detail.

The intended commercial batch size for the finished product is defined. Batch formula has been provided.

Process validation

Commercial-scale process B FP batches were manufactured as the process performance qualification (PPQ).

With regard to shipping, the process is briefly described and data are provided supporting that the shipping procedure can be considered qualified.

Control of excipients

Excipients were selected to ensure quality and stability of zolbetuximab FP. All excipients are of compendial degree (Ph.Eur.). No excipients of human or animal origin and no novel excipients are used in the FP. The numerical references of the specific Ph. Eur. documents are provided. Analytical validation is not required for excipients tested in accordance with current compendial method. These compendial analytical procedures should be verified for their suitability under conditions of use commensurate with the complexity of the test method. Analyses of the excipients were successfully conducted according to the respective Ph. Eur. requirements. All results obtained were compared with the results of the manufacturer's CoAs and were found to fulfil all requirements of the respective release specification. This is acceptable.

2.4.3.3. Product specification, analytical procedures, batch analysis

Control of finished product

Specifications for zolbetuximab FP are set in accordance with ICH Q6B. All relevant characteristics of zolbetuximab FP (identity, content, potency, purity, impurities and safety) are adequately covered.

Potency is controlled by two different assays, ADCC and CDC reflecting the MoAs. The method descriptions and the method validation summaries were updated to include in-house method identification numbers for the non-compendial methods. The statistical approaches for determining the protein content and the osmolality specifications were presented.

Compendial analytical methods are performed in accordance with Ph. Eur. With regard to non-compendial methods it is referred to the AS section as the methods are the same with minor adaptions except the methods solely used for FP testing, which are briefly described. The compendial methods have been verified at the receiving laboratory/ies. For non-compendial analytical procedures, the procedures for the AS have been validated and the difference between the AS and FP is only buffer composition. Therefore, these procedures for the FP can be regarded as validated by confirming specificity of these procedures for the FP.

No new impurities known to form during the manufacture and storage of the zolbetuximab finished product have been detected. Also, for potential nitrosamine impurities, the risk assessment conducted for FP including review of all potential sources of nitrosamines in the components used in production revealed a negligible risk of contamination of FP with nitrosamine impurities.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities (EI). The risk of potential elemental impurities sources was considered low, which can be agreed. The information on the control of elemental impurities is satisfactory.

Batch analysis

Batch data for the batches manufactured by Process A and by Process B were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

Reference standard used for finished product testing is the same as for the active substance.

Container closure system

Zolbetuximab finished product is filled in 20 mL clear Type I glass vials stoppered with a 20 mm lyophilization stopper.. An aluminium seal is used to crimp onto the pre-stoppered vial. Components in contact with the product fulfil the Ph.Eur. requirements for glass containers for pharmaceutical use and elastomeric closures for injection. The Applicant provided data from extractable/leachable studies and also a risk assessment for the presence of some leachable compounds that were detected above limit of quantitation.

2.4.3.4. Stability of the product

Pre-PPQ batches manufactured with Process B at the commercial site are stored at long term, accelerated and stressed conditions for primary stability. Stability data for up to 48 months at the long-term storage condition are provided. The pre-PPQ batches can be considered representative, considering the comparability of zolbetuximab finished product (FP) batches across clinical trial material, primary stability

study, and process performance qualification. In addition, stability data up to 18 months at the long-term storage condition are provided for the PPQ batches. For the PPQ batches 12 months stability data obtained at accelerated conditions (completed) are provided too.

The proposed shelf life of 48 months (4 years) at 2 to 8°C as stated in the SmPC is considered acceptable and supported by real time stability data obtained with representative pilot-plant scale batches and in addition by data obtained under accelerated and stress conditions which indicate a favourable stability of zolbetuximab FP.

The lyophilized finished product is not significantly susceptible to exposure of normal room light conditions however the finished product is stored in carton boxes.

2.4.3.5. Post approval change management protocol(s)

N/A

2.4.3.6. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.. No material of bovine origin is added during fermentation of zolbetuximab. The MCB is free from TSE-risk substances.

Virus safety

The cells used for production of zolbetuximab have been extensively screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB of zolbetuximab with the exception of intracellular A-type retroviral particles which are well known to be present in hamster CHO cells. However, this is acceptable since there is sufficient capacity within the manufacturing process of zolbetuximab for reduction of this type of viral particles. Therefore, there are no concerns for the use in the production process of zolbetuximab. The purification process of zolbetuximab includes several steps that contribute to the virus safety of zolbetuximab. The effectiveness of these steps has been sufficiently demonstrated.

In summary, the virus safety of zolbetuximab is sufficiently demonstrated.

2.4.3.7. GMO

Not applicable

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Zolbetuximab is a new, highly purified chimeric (mouse/human IgG1) monoclonal antibody directed against CLDN18.2, a protein located in the tight junction in the epithelium of normal gastric tissue as well as in many human cancers.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The manufacturing process of zolbetuximab active substance and its controls are adequately described in the dossier. During the assessment, a Major Objection (MO) on the GMP status of the active substance manufacturing site was raised. Following an inspection, the GMP compliance of this site was confirmed. Some issues needed clarification and were adequately addressed by the Applicant.

The manufacturing control strategy for zolbetuximab consists of several steps: identification of CQAs of AS, risk analysis of process steps and process parameters that could affect CQAs, process characterization studies, establishment of CPPs and establishment of control strategies to ensure AS consistently meets specifications. In general, these steps are adequately described.

Validation has been performed by historical data assessment with respect to the impact of process performance on product quality attributes, followed by a risk assessment to establish and justify the operational ranges and in-process tests proposed for commercial manufacturing. A formal process validation at manufacturing scale with consecutive batches was successfully completed indicating that the process is capable of yield a product of satisfactory quality. A post-approval stage of process validation will be performed over the duration of the product lifecycle. The approach is considered adequate.

Manufacturing process development from the initial Process A to the commercial Process D has been documented and AS analytical comparability along the development stages has been demonstrated.

Characterization was conducted applying state-of-the-art methods and a detailed description of the physicochemical and biological characteristics of zolbetuximab is presented. The characterization is found adequate.

Evaluation of process-related impurities clearance was performed and the safety risk was assessed. Characterization of product-related impurities is described and process capabilities for product-related impurities clearance are evaluated.

The proposed strategy for the control of the zolbetuximab active substance is comprehensive and generally considered adequate to ensure quality and consistency during manufacture.

A two-tiered reference standard approach consisting of a primary and a working reference standard representative of commercial process D material is well described. In general, the proposed approach is endorsed.

The proposed container-closure system for the AS storage is also well described generally, including product-contact materials, as well as relevant product-specific information regarding the potential leachables and extractables. Regarding AS stability, the protocol is adequate and complies with ICH Q5C requirements.

Vyloy finished product 100 mg/vial is supplied as a sterile, preservative-free, white to off-white lyophilized powder, in a single-dose vial.

The FP manufacturing process is adequately described and validated. FP stability studies have been provided and support the proposed FP shelf-life. Adventitious agents control strategy is considered appropriate.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

In conclusion, the dossier presented by the Applicant for the Marketing Authorisation Application for Vyloy (zolbetuximab) contains adequate and complete information, to support the approval of this application.

2.5. Non-clinical aspects

2.5.1. Introduction

Zolbetuximab (IMAB362) is a chimeric (mouse/human) antibody with human IgG1 constant regions directed against the tight junction molecule claudin 18 splice variant 2 (CLDN18.2).

CLDN18.2 is a transmembrane protein that is exclusively expressed on epithelial cells in gastric mucosa; its expression is maintained in the course of malignant transformation and therefore frequently expressed on the surface of human gastric cancer cells. In addition, CLDN18.2 is aberrantly expressed in oesophageal, pancreatic and lung adenocarcinomas.

Zolbetuximab binds to extracellular domain 1 of human CLDN18.2 and exerts the anti-tumour effects primarily through ADCC and CDC. Chemotherapy increases CLDN18.2 expression which further enhances zolbetuximab-induced cytotoxicity.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro binding

Using flow cytometry, zolbetuximab was shown to stain HEK293 cells transduced to express human CLDN18.2, but not CLDN18.1, demonstrating specificity of zolbetuximab for the splice variant CLDN18.2. The affinity of zolbetuximab to HEK-293 cells expressing human CLDN18.2 is approx. 2.3 nM. The affinity to gastric cancer cells KATO-III and NUCG-4 is slightly lower (11 nM, 17.3 nM), which may be due to the lower expression of CLDN18.2 on these cells.

The epitope recognised by zolbetuximab was identified in the CLDN18.2 extracellular loop 1 (amino acids 28 to 65). The amino acid sequence in this region is identical in humans and CLDN18.2 orthologues from non-clinical species (cynomolgus, rhesus, dog, mouse, rat). Only rabbits have a single amino acid change. Given the sequence identity in the zolbetuximab epitope, the binding affinity of zolbetuximab to cells expressing the cynomolgus or the murine CLDN18.2 orthologue was comparable to that for human CLDN18.2, i.e. low nM range.

In vitro function

Possible modes of action of zolbetuximab were evaluated in human cell systems in vitro. Given that zolbetuximab carries a human IgG1 Fc-part, it is expected to mediate Fc-dependent effector functions. This was confirmed in vitro. In the presence of human PBMC as effector cells, zolbetuximab induced Ab-dependent lysis of CLDN18.2-expressing tumour cells, while no lysis was induced against CLDN18.2-negative cells. The ADCC activity correlated inversely with the level of CLDN18.2 expression by the tumour cells, lower EC50 values were observed at higher epitope levels. The phenotype of the FcγRIIIa expressed by the effector cells (V/V, F/F) did not significantly affect % maximum cell lysis induced by zolbetuximab nor the EC50 values. In the presence of human serum as a source of complement, zolbetuximab induced specific lysis of CLDN18.2-positive tumour cells. The % maximal lysis induced correlated with the expression level of CLDN18.2.

In addition, zolbetuximab mediated inhibition of tumour cell growth in a BrdU proliferation assay, in the absence of effector cells or complement. The exact mechanism of the tumour growth inhibition was not evaluated. However, when tumour cells were incubated with zolbetuximab-coated beads, leading to

cross-linking of CLDN18.2 on the cell surface, tumour cells underwent apoptosis as demonstrated in a TUNEL assay and a Caspase 3/7 activity assay.

The capability of zolbetuximab to induce Fc-dependent effector functions (i.e. ADCC and CDC) against CLDN18.2-positive cells was also evaluated in cynomolgus and murine cell systems since these species were selected for non-clinical safety testing of zolbetuximab. In the presence of cynomolgus PBMC or cynomolgus serum, zolbetuximab induced ADCC and CDC against HEK293 transfectants expressing cynomolgus CLDN18.2 although with a slightly reduced activity compared to a fully human system. The differences in ADCC activity in monkey and human systems (HEK cells transfected with cynomolgus or human CLDN18.2 in the presence of PBMC or serum from monkey and human donors, respectively) could be due to a lower binding affinity of zolbetuximab to monkey FcRs compared to human FcRs or to differences in the expression levels of the different CLDN18.2 orthologues on the cell surface of the transfected HEK293 cell line. However, the causes for the different ADCC activities were not investigated. The differences in CDC activity could be due to lower expression of cyCLDN18.2 on the cell surface of the HEK293 transfected cell line.

Since mice are phylogenetically more distinct from humans than NHP, the in vitro evaluation of the zolbetuximab Fc effector functions in murine system was more comprehensive and included also a murine version of zolbetuximab, i.e. muMAB362 with a murine IgG2a Fc part (equivalent to human IgG1). It was shown that zolbetuximab bound more efficiently to cells expressing human FcγRIIIa while muMAB362-IgG2a bound showed stronger binding to cells expressing murine FcγRIIIa, and vice versa. In an ADCC assay with target cells expressing murine CLDN18.2 and mouse splenocytes as effector cells, both zolbetuximab and muMAB362 induced ADCC. Zolbetuximab-induced CDC against cells expressing human CLDN18.2 was lower in the presence of mouse serum as source of complement, than in the presence of human serum. This may be explained with low complement activity of mice compared to other laboratory animals or humans.

In vitro combination with chemotherapeutic agents

The effect of chemotherapeutic agents in combination with zolbetuximab was evaluated in different assay formats in vitro. Different chemotherapeutic regimens were employed, i.e. epirubicin/oxaliplatin/5-FU (EOF), 5-FU/leucavorin/oxaliplatin (FLO) or 5-FU/oxaliplatin (FO). These chemotherapeutic agents are representative of the classes of therapeutics used in the clinic for treatment of gastric or gastro-oesophageal junction (GEJ) adenocarcinoma. Incubation of gastric cancer cells (NUGC-4 and KATO-III) with EOF or FLO induced an increase in cell surface expression of CLDN18.2. Consistent with these findings, zolbetuximab-induced ADCC and CDC was enhanced in gastric cancer cells pre-treated with EOF or FU. The increase in % specific killing was minimal, however, the zolbetuximab EC50 was clearly reduced. In addition, zolbetuximab-induced apoptosis of NUGC-4 cells was clearly enhanced in the presence of either 5-FU or EOF. These in vitro data provide a pharmacologic rationale for the combination of zolbetuximab with fluoropyrimidine- or platinum-containing chemotherapeutics in the clinic.

In vivo studies

Prior to in vivo efficacy studies, the in vivo tissue binding of zolbetuximab was determined ex vivo. In nude mice bearing CLDN18.2-expressing human tumour cells, zolbetuximab bound with strong intensity to the tumour tissue and with a lower intensity to normal stomach tissue. No zolbetuximab binding was detectable in kidney, pancreas, spleen, liver and lung. Although the study evaluated only a limited number of normal tissues for zolbetuximab binding, the data indicate that zolbetuximab binding in vivo is target-specific and limited to tissues expressing CLDN18.2.

The anti-tumour efficacy of zolbetuximab monotherapy was investigated in nude mice bearing established human NUCG-4 tumours. In this model, twice weekly treatment with zolbetuximab at approx. 8 mg/kg IV/IP slowed the tumour growth compared to that in control animals administrated saline. Also,

survival of zolbetuximab-treated animals was only minimally prolonged compared to survival in the control groups. While the anti-tumour effect of zolbetuximab in this model is acknowledged, the effect of zolbetuximab is not overwhelming.

Consequently, the in vivo anti-tumour efficacy of zolbetuximab was tested in combination with chemotherapeutic agents. In immuno-deficient nude mice inoculated with NCI-N87-CLDN18.2 tumours, zolbetuximab in combination with EOF or FLO regimens slightly improved control of tumour growth (at Day 38), compared to chemotherapy alone or zolbetuximab alone. In nude mice inoculated with NUGC-4 tumours, zolbetuximab in combination with EOF chemotherapy improved tumour growth inhibition (at day 14) compared to saline and also to zolbetuximab alone; in addition, median survival was slightly prolonged in the combination group. In these xenograft tumour models in immunocompromised nude mice, the anti-tumour effect of the combination of zolbetuximab with chemotherapy was slightly but not significantly enhanced compared to the effect of zolbetuximab alone or chemotherapy alone.

In the tumour model of syngeneic gastric mouse tumour in immunocompetent NMRI mice, the effect of zolbetuximab or EOF monotherapy on tumour growth compared to saline control animals was limited. However, the zolbetuximab/EOF combination treatment induced significantly enhanced tumour growth inhibition (Day 17) and also prolonged survival (up to Day 87) compared to the monotherapy arms. In tumours from the combination therapy group, an increase in percent infiltrating CD8+ T cells was observed. These results were reproduced in the same tumour model using zolbetuximab and OF chemotherapeutics. On Day 16, tumour growth inhibition in mice treated with the zolbetuximab/OF combination was significantly greater than the inhibition after monotherapy treatment. In addition, infiltration of tumours by CD8+ T lymphocytes was highest in mice that had received the combination therapy.

Taken together, the in vivo data in mouse models bearing either CLDN18.2-positive human tumours or syngeneic mouse gastric tumours indicate that zolbetuximab monotherapy has limited anti-tumour activity, while zolbetuximab in combination with chemotherapy mediates clinically relevant tumour growth inhibition. Also, these data support the combination of zolbetuximab with fluoropyrimidine- or platinum-containing chemotherapeutics in the clinic.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamic studies are not described. However, Fc-dependent effector functions, i.e. ADCC and CDC are part of the zolbetuximab mode of action. Studies evaluating these functions are described in the primary pharmacodynamics section. Binding to Fcγ receptors and C1q is part of the characterisation of the active substance and provided in module 3.

2.5.2.3. Safety pharmacology programme

The effects of zolbetuximab on the CNS were evaluated in a dedicated study in NMRI mice. After a single IV administration, zolbetuximab at up to 100 mg/kg did not affect any of the neuropharmacological parameters assessed in the Irwin Test.

Effects of the cardiovascular and respiratory system were evaluated as part of the 4-week toxicity study in cynomolgus monkeys. No effects on ECG, blood pressure and respiratory rate were observed at up to 100 mg/kg administered by IV injection.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic studies evaluating zolbetuximab in combination with chemotherapeutic regimens are described as part of the primary PD studies. This is considered sufficient.

2.5.3. Pharmacokinetics

The PK/TK of zolbetuximab was assessed in cynomolgus monkeys and in mice. Both represent relevant species with target binding. In the pharmacokinetic studies, only intravenous administration of zolbetuximab was investigated which represents also the route of administration in the clinic. One dedicated single dose pharmacokinetic study was conducted in cynomolgus monkey in which further two different drug substance batches were compared with respect to pharmacokinetics. The repeat dose studies in mice and cynomolgus monkeys represent the pivotal toxicology studies, and the PK/TK of these studies are further discussed in the toxicology section.

Bioanalytical methods

Different bioanalytical methods were developed throughout the development.

For detection of zolbetuximab, a qualified ELISA was used with mouse serum and a qualified flow cytometry assay for detection in cynomolgus serum. Both methods are considered suitable for use. A validated ECLIA method was used for detection of zolbetuximab in mouse, cynomolgus and ferret serum as part of the TK and toxicity studies performed . The method is considered adequately validated for use in the different matrices.

For detection of ADA in both mouse and cynomolgus serum, a qualified ELISA method was used initially. The method is considered suitable for use. A validated bridging ECLIA was used for determination of ADA in mouse and cynomolgus serum in studies performed . The ECLIA method is considered adequately validated for use in the different matrices.

Studies in mice

Zolbetuximab was administered at 100, 200 and 300 mg/kg one weekly for 13 weeks. Pharmacokinetic parameters determined at day 1 and day 92 revealed an almost dose proportionally increase of Cmax and AUC with a slight accumulation. The half-life was slightly decreasing with increasing dose which is somehow unexpected. However, it was approximately 4.8 days on day 1 and 10 days on day 92. ADAs might been present in 11 samples, however given the random distribution, the low levels, and the zolbetuximab serum levels it is not expected that exposure was significantly impaired.

Studies in cynomolgus monkeys

Single-dose PK/TK studies

In a single dose PK study, 10 mg/kg zolbetuximab was administered intravenously. Cmax was 287 µg/mL and a half-life of approximately 9 days was noted. Further, PK parameters from different zolbetuximab drug substances manufactured at two different sites were compared. Five monkeys each were dosed with 10 mg/kg and PK parameters were evaluated weekly up to day 56. In summary, no difference was noted in PK parameters or ADA production among the groups.

Repeat-dose TK studies

Zolbetuximab was administered intravenously at 10, 30 and 100 mg/kg once per week for 4 weeks. An almost dose-proportional increase was noted for Cmax and AUC. A very slight accumulation was visible on day 29. No differences between the sexes were noted and no ADAs were detected.

Distribution

No specific studies were conducted with regard to distribution. This is acceptable and in accordance with the scientific guideline ICH S6(R1) in which no tissue distribution studies are considered necessary.

Metabolism

No dedicated studies on the metabolism/catabolism of zolbetuximab have been performed. Omission of metabolism studies is acceptable and in line with ICH S6(R1), as monoclonal antibodies are expected to be catabolised as endogenous proteins.

Excretion

No dedicated excretion studies were conducted with zolbetuximab, which is in line with ICH S6(R1) and considered acceptable. IgG antibodies are usually not excreted renally due to their large size and are catabolizes into peptides and amino acids.

Pharmacokinetic drug interactions

The omission of non-clinical PK drug-drug interaction (DDI) studies is adequately justified and accepted. No significant influence on the cytochrome P450 system is expected.

Other pharmacokinetic studies

No other pharmacokinetic studies were conducted. This is considered acceptable, since no other pharmacokinetic studies are considered necessary.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Toxicity of zolbetuximab was assessed in single dose toxicity studies in mice. Herein, mice received up to 0, 1, 10, 50 or 100 mg/kg zolbetuximab by IV administration. Zolbetuximab was well tolerated. No findings with regard to toxicity were observed. Toxicokinetics were evaluated, however the presence of anti-drug antibodies (ADA) was not investigated. In control groups mice further received other monoclonal antibodies at different dose levels. All control antibodies are not reactive in mouse and no signs of toxicity were observed. These control groups are considered unnecessary since they do not add value for safety assessment and are inappropriate for toxicology studies. Of note, serum IgG level in the group treated with a control antibody (Remicade) were twice as high as compared to respective zolbetuximab dose level, the reason why is unclear.

Further, single dose toxicity was assessed in cynomolgus monkeys. Animals were dosed with 50 mg/kg Zolbetuximab and 17 days later 150 mg/kg Zolbetuximab was administered intravenously. Since the same animals were dosed twice, it is rather a dose escalation than a single dose toxicity study. No signs of toxicity were noted. One animal had emesis on several days after the second dose. Since haemorrhagic foci were observed at necropsy in the stomach and emesis is a known side effect of zolbetuximab, emesis in this animal could be treatment related.

2.5.4.2. Repeat dose toxicity

Repeat dose toxicity studies were conducted in mice and cynomolgus monkeys.

Studies in mice

Initially, NMRI mice were treated once weekly with 30 or 100 mg/kg zolbetuximab by IV injection for a total of up to 5 injections. Rituximab (100 mg/kg), PBS + arginine buffer and untreated animals were included as controls. Further, one group was treated with murine IgG2a-zolbetuximab, which corresponds to human IgG1 with respect to Fc effector function. Its ADCC and CDC activity was proven for murine variant IgG2a from zolbetuximab (refer to pharmacology section). No effects with regard to clinical signs, local tolerance, body weight, water consumption, immunophenotyping and histopathology were noted. Further, one group of mice were treated with murine variant IgG2a from Zolbetuximab, representing human IgG1 in mice with regard to Fc effector function. One animal of the murine IgG2a group and one from the vehicle group died prematurely, both were not considered to be test item-related. Slight changes in haematology are of unknown relevance given the number of analysed animals. The presence of ADAs was not investigated, therefore exposure may be impaired in some animals but in general IgG serum levels do not suggest strong impairment of exposure.

A dose range finding study in mice was conducted to select the dose levels for the 13-week subchronic toxicity study. The study was conducted in GLP compliance. Herein, test article batches from Process A and Process B were included in part 1 to compare the toxicity and toxicokinetic profile between test and reference item. With regard to toxicokinetics, no changes were noted between the sexes. Since Cmax levels of ca 1700 µg/mL on day 1 and 3000 µg/mL on day 15 were observed, a slight accumulation was observed. The serum concentration of group 2 which were treated with reference item was ascending at 6 hours compared to the previous time point, which is unexpected given the route of administration. However, this is possibly caused due to the high standard deviation and the linear scale instead of logarithmic scale. The mean terminal serum elimination half-life was ca 19 hours on day 1 and ca 134 hours on day 15. No significant changes were noted for either the toxicokinetic profile or signs of toxicity between the two test articles, confirming comparability of process A and process B batches. The comparability was further demonstrated with regard to pharmaceutical quality (refer to quality assessment report). In part 2, doses of 100, 200 or 400 mg/kg of the test item were administered once a week. A slight reduction in the number of leucocytes was observed in animals treated with 400 mg/kg compared to animals treated with 100 mg. However, no control group was included, values were still within historical control range. No other significant findings were noted. The presence of ADAs was not analysed.

A 13-week subchronic toxicity study was conducted in mice. Zolbetuximab was applied once weekly by IV injection to NMRI mice at doses of 100, 200, or 300 mg/kg for 13 weeks. In addition, another group was treated with 300 mg/kg Zolbetuximab (reference item). Further some mice received the murine variant of zolbetuximab which corresponds to human IgG1 with respect to Fc effector function. Mortality, clinical signs, local tolerance, ophthalmology, body weight, food consumption, haematology, clinical chemistry, urinalysis, organ weights, macroscopic and microscopic examinations and standard parameter of immune toxicity were monitored. No significant changes were noted for animals treated with zolbetuximab, therefore the NOAEL was set to the highest tested dose, 300 mg/kg. This is agreed. No differences were noted between test or reference item, demonstrating biological comparability between the two batches. Importantly, no macroscopic or microscopic changes were noted at all. Nonetheless, one mouse (animal 211) treated with zolbetuximab (200 mg/kg) was found dead on day 87. The animal was part of the satellite group for toxicokinetics and no histopathological analysis was performed, thus cause of death for this animal was not established. Taking into account overall data from the toxicity studies, death of this animal is likely coincidental.

The toxicokinetic evaluation demonstrated a dose-related linear exposure in serum levels and AUC. The half-life was 68 – 88 hours on day 1 and ca 200 hours on day 92. No accumulation with time was noted. No significant changes were observed between the sexes. Also, no differences between the test item and reference item were observed. ADAs were confirmed for one animal and another 10 samples were putatively positive for ADAs. Nonetheless, no effect of exposure was obvious. In the recovery

period no ADAs were detected at all. In general, the toxicokinetics were as expected and suggest sufficient exposure of the animals.

A group of mice received the murine variant of zolbetuximab which exerts comparable Fc effector function to human IgG1. In this group, one animal died after the forth administration and the death is considered to be test article related. In addition, other animals had clinical signs of immune reactions. Since the first two applications of the murine variant were well tolerated, and symptoms occurred with the third application directly after administration and increased in severity, an immune reaction of allergic reaction is considered likely. Pre-treatment with antiallergic/ immune suppressive medication reduced the severity and incidence of symptoms. The observed allergic reactions are in accordance with substantially higher impurity content of Protein A, Host Cell Protein and DNA present in the murine variant compared to zolbetuximab.

Studies in cynomolgus monkeys

A 4-week, repeat-dose toxicology study was conducted in cynomolgus monkeys. Animals received 10, 30 or 100 mg/kg Zolbetuximab once weekly by intravenous injection for a total of 5 administrations. The group size was 3 animals per sex per group with a total of 24 animals and no recovery period was foreseen which is acceptable since no toxicities were observed.

Zolbetuximab was well tolerated. No test item-related influences were noted for the male and female animals treated with 10, 30 or 100 mg/kg on the local or systemic tolerance, body weight and body weight gain, food and drinking water consumption, the ECG, the circulatory functions and the respiratory rate. Further the eyes and optic region, the auditory functions, haematological and biochemical parameters, the urinary status as well as the immunoglobulins and cytokines were not affected. Additionally, necropsy, organ weights, bone marrow evaluation and histopathology revealed no test item-elated effects. Emesis was observed in each 1 of 3 male animals treated with 10 or 30 mg/kg zolbetuximab on test day 8, being non-severe and thus was not considered adverse. Since emesis is a known side effect of zolbetuximab, this finding is probably treatment related. However, in histopathologic examinations some inflammatory lesions occurred in the stomach, but also in the control group and also for other organs. A NOAEL was not formally set in the study report, but in the nonclinical overview a NOAEL of 100 mg/kg (highest dose tested) was determined.

Immunohistochemical examinations were conducted with tissue obtained from the animals. This is rather unusual for toxicity studies. However, as expected, CLDN18.2 protein expression was absent in kidney, liver, heart, lung and pancreas but expressed in stomach tissue and weakly stained in duodenum tissue, presumably the Brunner glands. Further, the tissues were stained for zolbetuximab in order to evaluate whether there was accumulation in stomach tissue of the therapeutic antibody. Kidney and liver tissue were not evaluable due to technical issues. Zolbetuximab was detected in the blood of all organs of the high dose group. Further, zolbetuximab was detected in heart tissue of the high dose group (100 mg/kg) and in some animals from the low dose group (10 mg/kg). Staining was not expected but it was located in the cytoplasm. Since usually antibodies do not enter the cell, this form of staining is probably unspecific and not considered to be relevant with regard to safety. In addition, no zolbetuximab-related adverse findings were noted in the microscopic examination of the heart. Therefore, it is concluded that the staining of the heart is not of clinical relevance. In stomach tissue positive staining was observed in treated animals and samples were also partly positive in the control group. Since the control group was not treated with zolbetuximab, no staining is expected at all. However, staining in the control stomach tissue was likely unspecific.

In the toxicokinetics, a more or less linear dose-related exposure of the animals to zolbetuximab with regard to Cmax and AUC was noted. No differences between the genders were obvious. No ADAs were detected in the monkeys, suggesting that exposure was not affected. Again, as noted in the dose-range finding study in mice, the PK profile is unexpected since an elevation in serum concentration was

noted 6 hours after IV administration in the high dose group and slightly also in the medium dose group. An explanation for this deviation might be rather high standard deviation and the limited number of animals in the groups.

Cynomolgus monkeys (3/sex/group) were dosed with a single IV injection of 10, 30 or 100 mg/kg zolbetuximab in order to investigate the toxicokinetics using validated assays for toxicokinetics and ADA detection. Animals were observed until day 56, and blood samples for toxicokinetics were taken. Further, clinical signs, body weight and food consumption were observed. No toxicities were noted on the investigated parameters. With regard to toxicokinetics, anti-drug antibodies were detected at all dose levels, being highest at 30 mg/kg and 10 mg/kg. However, titre of ADA had no obvious influence on exposure. In this study, ADAs were detected in 13/18 animals but not in the 4-week toxicity study. This is rather unexpected since repeated administration could trigger ADA formation in contrast to a single administration. While different methods (ELISA or ECLIA) were used in the two studies, the difference in time of blood sampling (Day 57 vs. Day 1 or Day 5 after dosing) and the absence or presence of zolbetuximab interfering with ADA detection may be the reason for the discrepancy in ADA detection between the two studies.

This single-dose study was conducted to provide complementary toxicokinetics in compliance with GLP since toxicokinetics in the 4-week repeat dose toxicity study was analysed in a non-GLP site. This study is considered unnecessary, since it does not confirm sufficient exposure in the pivotal 4- week tox study, and therefore does not add value. Nonetheless, zolbetuximab Cmax levels in both studies are in a comparable range (compared to day 1 of the 4-week toxicity study). Also AUC values that cover the same period in both studies ($AUC_{0\text{-}168h}$ and $AUC_{0\text{-}24h}$) were comparable and indicate the reliability of the TK data from the 4-week toxicity study.

Interspecies comparison

Serum Cmax and AUC values at the NOAEL in pivotal nonclinical toxicity studies and their exposure multiple relative to the human dose (600 mg/m²) were calculated. Serum AUC at the NOAEL was at 11-12-fold based on clinical data, and 6–7-fold based on the new Pop-PK model. Safety margins are considered sufficient.

2.5.4.3. Genotoxicity

In line with ICH S6(R1), genotoxicity studies are not warranted for mAbs.

2.5.4.4. Carcinogenicity

In line with ICH S9, omission of carcinogenicity studies is acceptable. Zolbetuximab is intended for treatment of patients with advanced cancer, also in combination with chemotherapeutics targeting fast growing cells.

2.5.4.5. Reproductive and developmental toxicity

No dedicated studies regarding fertility and early embryonic studies were conducted which is in line with guideline ICH S9. Male and female reproductive organs were however investigated by histopathology in the 4-week toxicity study with cynomolgus monkeys and in the 13-week toxicity study with mice. No abnormalities were observed.

The effect of zolbetuximab on embryo-foetal development (EFD) was evaluated. In line with ICH S9, studies on fertility and early embryonic development and studies on pre- and post-natal development

are not warranted for pharmaceuticals intended for treatment of patients with advanced cancer. Omission of these studies is therefore acceptable.

EFD studies were conducted in one species only. According to ICH S9, this is acceptable for biopharmaceuticals. In these studies, zolbetuximab was administered to pregnant NMRI mice on GD6 and GD11, a period intended to cover embryonic development from implantation to closure of the hard palate. C-sectioning was performed on GD18. In the range-finding study, there were no zolbetuximab-related changes noted in dams or on foetal parameters up to the highest dose, 300 mg/kg IV. TK were not assessed as part of this exploratory study.

In the pivotal, GLP-compliant EFD study, zolbetuximab was administered at 0, 100 or 300 mg/kg IV. In this study, Cmax increased dose-proportionally and AUC120h less than dose-proportionally between 100 and 300 mg/kg dose levels. On GD18, 8 days after the 2nd dose, zolbetuximab concentration in dams was reduced to approx. 8-10 µg/ml while zolbetuximab concentrations in foetal serum were 11.2 and 8.5x higher than those seen in dams at that time. These data indicate that foetuses were exposed to zolbetuximab. Anti-drug antibodies were not detected on GD18 in any group. It is however noted that zolbetuximab concentrations were above the drug tolerance level of the ADA assay.

Consistent with the findings of the range-finding study, there were no zolbetuximab-related changes in clinical signs, body weight, body weight gain, food consumption, gross pathology, the number of corpora lutea or the number of implantations in dams treated at doses up to 300 mg/kg. In addition, there were no zolbetuximab-related changes in any of the foetal / placental parameters evaluated (number of live foetuses and of embryofoetal deaths, rate of post-implantation loss, sex ratio, foetal body weight, placental weight) at up to 300 mg/kg. Of note, there were no zolbetuximab-related external, placental, visceral, or skeletal abnormalities or variations.

Thus, the NOAEL of zolbetuximab for maternal and embryo-foetal development is 300 mg/kg. The exposure margin achieved at this dose was approx. 6.2x the human exposure (based on AUC) at the recommended dose of 600 mg/m2.

Wording on the lack of reproductive and developmental toxicity findings is included in section 4.6 and 5.3 of the SmPC.

2.5.4.6. Toxicokinetic data

Toxicokinetic data are discussed in the sections above concerning the single and repeat dose toxicity studies.

2.5.4.7. Tolerance

Local tolerance observations were incorporated in the toxicology studies. This is acceptable, no dedicated studies are warranted. No unexpected findings were reported.

2.5.4.8. Other toxicity studies

Since vomiting was observed in clinical studies and some cynomolgus monkeys treated with zolbetuximab, mechanistic studies were conducted to assess emetic potential. Given that mice are not capable of vomiting, the ferret was chosen as species since it is known as gold standard for emesis studies.

Zolbetuximab was administered to 4 animals, 2 animals died shortly after administration and the remaining 2 ferrets had emetic activity. Further, one male died on day 4 after receiving control but this

death is considered to be related to the surgical procedure. However, no clinical signs were observed in the remaining animals that received additionally control medication on days 16 and 21. Tissue from the ferrets was analysed retrospectively for Cldn18.2 expression by RT-PCR and TCR. Although there are some limitations due to limited information about ferret genomic status, results suggest that Cldn18.2 is expressed in the stomach and not in other ferret tissues tested. Due to the poor tissue quality, immunohistochemistry stainings were partly unspecific, but expression of CLDN18.2 protein was detected in the stomach and duodenum of the animals. In conclusion, since ferrets are generally a sensitive species and zolbetuximab was given as 30 minutes infusion, it is conceivable that mortality was related to bacterial infection.

Next, a dose range finding study was conducted. Ferrets were administered 0.2, 1, 5 and 20 mg/kg zolbetuximab. At 1 mg/kg and higher, clinical signs of retching and vomiting were observed, therefore the dose of 1 mg/kg was recommended for the subsequent studies.

The relationship of emesis and histopathology of the stomach was investigated in a third study. Herein, zolbetuximab at 1 mg/kg was administered and the animals were sequentially sacrificed. Results suggest that the surface mucous cell of the stomach is damaged after administration of zolbetuximab and that the damage to the gastric mucosa is associated with the onset of vomiting in ferrets. The assay for zolbetuximab serum concentration was adequately validated.

The effects of antiemetics (dexamethasone, ondansetron, fosaprepitant, olanzapine, and combination of these four antiemetics) or ondasetron and fosaprepitant were evaluated on the zolbetuximab-induced emesis and on the gastric mucosa in 4- to 5-month-old male ferrets.

In general, antiemetics tended to reduce emesis frequency and alleviate macroscopic abnormalities. In study 10844, the combination of all four antiemetics seemed to be most effectively; in study 8951-TX-1005 fosaprepitant and the combination fosaprepitant and ondasetron apparently were most effective; however, clinical signs and histopathology was very individual and in general limited to the low number of animals.

In conclusion, the emesis studies conducted in ferrets confirmed the hypothesis that zolbetuximab induces damage to the gastric mucosa, which results in emesis. Antiemetic medication did not influence the cellular damage but somehow alleviated the symptoms. However, these studies are considered unnecessary and the appropriate medication to reduce nausea and vomiting should be addressed in the clinic.

Antigenicity

The formation of anti-drug antibodies (ADA) was investigated in the toxicological studies and has been discussed in the sections above. Overall, the incidence of ADA formation was rather low and it is not expected that the exposure to the test article has been significantly impaired.

Immunotoxicity

No effects on the immune system were observed in the pivotal toxicity studies.

Dependence

Dependence studies are not applicable to a monoclonal antibody and no evidence for abuse potential is assumed for zolbetuximab.

Metabolites

Specific studies for major human metabolites (or isomers) insufficiently present in animals.

No metabolite studies were conducted with zolbetuximab which is in accordance with ICH S6(R1).

Studies on impurities

No impurities studies were conducted for zolbetuximab. However, impurities are well controlled at production level.

Other studies

The TCR conducted with human material revealed significant staining in the mucosal epithelium of stomach, which was expected and is in accordance with the literature. Other staining in liver, pancreas, skin and spleen was observed but was cytoplasmic in nature, thus not representing a concern with regard to safety since cytoplasmic staining is not of relevance in vivo. Further staining was more intense at higher antibody concentrations, indicating some tendency of unspecific staining. Positive and negative controls were included. Staining pattern was comparable between zolbetuximab manufactured at two different sites. The TCR was conducted by labelling zolbetuximab with FITC and detection of FITC with rabbit anti-FITC followed by DAB. Chromatograph and info about coupling ratio (flurochrome:protein) was provided.

In addition, tissues from humans, cynomolgus monkeys or mice were stained with zolbetuximab or murine surrogates (murine IgG1 or IgG2a backbone). Staining was restricted to the mucosal epithelium of the stomach. The staining of other tissue was variable at the different conditions but either unspecific or cytoplasmatic in nature. This tissue cross reactivity further confirms the conserved structure of CLDN18.2.

Phosphoric acid is used as an excipient in the drug product. The applicant has provided a thorough justification supported by clinical data with authorized drugs that is considered adequate to support the safety of this compound in zolbetuximab drug product. Furthermore, published studies support the lack of genotoxic potential for phosphoric acid.

2.5.5. Ecotoxicity/environmental risk assessment

Zolbetuximab is a protein, which is expected to biodegrade in the environment and to not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), zolbetuximab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The applicant has provided a comprehensive pharmacology package. A thorough characterisation of the target CLDN18.2 was submitted. In both humans and non-clinical species, expression of CLDN18.2 was found to be limited to differential epithelial cells of the gastric mucosa. Relevant to the present application, CLDN18.2 expression remained in human gastric cancers. Importantly, the majority of patient-derived gastric and oesophagus adenocarcinomas, both primary and metastatic cancers, were CLDN18.2-positive.

The pharmacologic activity of zolbetuximab was adequately characterised. Binding specificity for CLDN18.2 was confirmed; the epitope recognised was identified in the 1st extracellular loop of CLDN18.2, a region that is highly conserved across species. The binding affinity of zolbetuximab to human CLDN18.2 was in the low nM range and was found to be comparable for cynomolgus and mouse CLDN18.2.

In vitro functional studies have demonstrated that zolbetuximab mediates Fc-dependent cytotoxic activity against target cells expressing CLDN18.2. Zolbetuximab induced both ADCC and CDC. In addition, zolbetuximab was found to induce tumour cell apoptosis. A comprehensive characterisation of zolbetuximab Fc-effector functions in murine system was also performed. In these in vitro studies, a murine version of the antibody with a mouse IgG2a part (muMAB362) was included. MuMAB362 bound strongly to murine FcγRIIIa but showed lower ADCC activity in the presence of mouse effector cells than zolbetuximab.

The anti-tumour activity of zolbetuximab in combination chemotherapy was also evaluated. The different chemotherapeutic regimens (EOF, FLO, FO) are considered representative of the classes of therapeutics used clinically for treatment of gastric or GEJ cancers. Chemotherapy induced an increase in CLDN18.2 expression on human cancer cells. Consistent with these findings, zolbetuximab-induced ADCC and CDC was enhanced in gastric cancer cells pre-treated with EOF or FO.

In vivo anti-tumour activity of zolbetuximab was evaluated in mouse xenograft models of human gastric cancer. Zolbetuximab monotherapy slowed tumour growth compared to that in saline-treated animals; survival of zolbetuximab-treated mice was minimally prolonged. While the anti-tumour effect of zolbetuximab in this model is acknowledged, the overall effect is not overwhelming.

Consequently, the in vivo anti-tumour efficacy of zolbetuximab was tested in combination with chemotherapeutic agents. In xenograft models in immunocompromised nude mice, the anti-tumour effect of the combination of zolbetuximab with chemotherapy was slightly but not significantly enhanced compared to the effect of zolbetuximab alone or chemotherapy alone. In immunocompetent mice bearing murine, CLDN18.2-positive gastric tumours, the zolbetuximab/chemotherapy combination treatment induced significantly enhanced tumour growth inhibition and also prolonged survival compared to the monotherapy arms. In tumours from the combination therapy group, an increase in percent infiltrating CD8+ T cells was observed. Thus, regardless of the model, only zolbetuximab in combination with chemotherapy mediated clinically relevant tumour growth inhibition. These data sufficiently support the combination of zolbetuximab with fluoropyrimidine- or platinum-containing chemotherapeutics in the clinic.

Pharmacokinetics

Pharmacokinetic and toxicokinetic analyses were conducted in mice and cynomolgus monkeys. Methods for pharmacokinetic and anti-drug antibody analyses are considered adequately validated for use. A single dose PK study in cynomolgus monkeys was conducted in order to compare the PK parameters from two different zolbetuximab drug substances manufactured at different sites. In summary, no difference was noted in PK parameters or ADA production among the groups, indicating that the PK profile is comparable although somehow limited given the small number of animals. In general, since comparability is not questioned on from the perspective of pharmaceutical quality (refer to quality assessment for details), animal studies are not appropriate and not considered necessary for assessing comparability.

In general, an almost dose proportional increase of Cmax and AUC was observed. No differences between the sexes or marked accumulation was noted. ADAs were present in some animals but obviously did not significantly influence the exposure to the test article.

Although some pharmacokinetic profiles were somehow unexpected, overall the pharmacokinetic and toxicokinetic studies performed for the present application are considered sufficient and support the IV route of administration.

Toxicology

To support the safety of zolbetuximab the applicant has presented a toxicology programme which is in line with current guidance (ICH S6(R1), ICH S9) and takes into account the scientific advice received from CHMP and national competent authorities. Selection of mice and cynomolgus as relevant species is considered adequate, based on the sequence homology and comparable tissue expression profile of human, cynomolgus and mouse CLDN18.2 and the comparable binding affinity of zolbetuximab to human, cynomolgus and mouse CLDN18.2.

Several single and repeat dose toxicity studies were conducted, not all of the studies are considered well-designed or necessary.

In single dose toxicity studies, mice were administered up to 100 mg/kg zolbetuximab intravenously. Zolbetuximab was well tolerated. In addition, in a dose escalation toxicity study in cynomolgus monkeys the animals received up to 150 mg/kg zolbetuximab. Except of vomiting of one animal, no signs of toxicity were noted.

Repeat dose toxicity studies were conducted in mice and cynomolgus monkeys. The sub-chronic toxicity study was conducted in mice. The study duration of 13 weeks with dosing once weekly is in line with guideline ICH S9 for the treatment of advanced cancer. Herein, mice received 100, 200 or 300 mg/kg zolbetuximab via intravenous route. No significant changes were noted for animals treated with zolbetuximab, therefore the NOAEL was set to the highest tested dose, 300 mg/kg. This is agreed. In addition, in this study one group was treated with the murine IgG2a variant of zolbetuximab. Clinical signs of immune reactions were noted that were in agreement with an allergic reaction. This is explained with the high impurity profile of the murine surrogate Ab.

In addition, cynomolgus monkeys received zolbetuximab at 10, 30 or 100 mg/kg once weekly for four weeks via intravenous administration. Zolbetuximab was well tolerated. Emesis was noted in few animals, was non-severe and thus was not considered adverse. However, since nausea and vomiting were observed in the clinic, this finding was probably test article-related. A NOAEL of 100 mg/kg was determined, the highest dose administered. This is endorsed. Using immunohistochemical staining, the applicant has also conducted studies to visualize zolbetuximab in selected tissues. Herein, zolbetuximab was detected in heart tissue of the high dose group (100 mg/kg) and in some animals from the low dose group (10 mg/kg). Staining of the heart is unexpected; it was found to be cytoplasmic. In addition, there were no zolbetuximab-related adverse microscopic findings of the heart. Thus, staining of the heart is not considered of clinical relevance. In stomach tissue positive staining was observed in treated animals and samples were also partly positive in the control group. The stomach staining of the control group was cytoplasmic and as such not toxicologically relevant.

As a conclusion, no toxicity or other zolbetuximab-related adverse effects on the cardiovascular, respiratory or central nervous systems was observed in mice administered zolbetuximab for 13 weeks at systemic exposures up to 7.0-fold the human exposure at the recommended dose of 600 mg/m^2 (based on AUC) or in cynomolgus monkeys administered zolbetuximab for 4 weeks at systemic exposures up to 6.1-fold the human exposure at the recommended dose of 600 mg/m^2 (based on AUC).

Since toxicokinetic analyses in the 4-week repeat-dose toxicity study in cynomolgus monkeys was conducted under non GLP conditions, a complementary single-dose toxicokinetic study in cynomolgus monkeys was performed in compliance with GLP. To allow comparison of the exposure the same AUC values (AUC0-24h; AUC0-168h) were calculated for both studies. Exposure based on AUC was found to be comparable in the two studies, supporting the reliability of the TK analysis of the 4-week repeat-dose toxicity study.

Safety margins were established based on human exposure determined with actual PK data and in addition, based on a Pop-PK model. Exposure multiple for serum AUC is 11 to12-fold based on clinical

data, and 6 to 7-fold based on the Pop-PK model that was updated during the procedure. The safety margins are considered sufficient.

No genotoxicity or carcinogenicity studies are warranted given the structure of zolbetuximab (monoclonal antibody) and the patient population (advanced cancer).

Reproductive and developmental toxicity studies were performed in mice. In line with ICH S9, only embryofoetal development was assessed; omission of studies on fertility and early embryonic development and on pre-/post-natal development is acceptable. Since studies to evaluate the effect of zolbetuximab on fertility have not been performed, the effect of zolbetuximab on male and female fertility is unknown.

In an embryo-foetal development toxicity study, where zolbetuximab was administered to pregnant mice during the period of organogenesis at doses resulting in systemic exposure approximately 6.2 times the human exposure at the recommended dose of 600 mg/m^2 (based on AUC), zolbetuximab crossed the placental barrier. The resulting concentration of zolbetuximab in foetal serum at Day 18 of gestation was higher than that in the maternal serum at Day 16 of gestation. Zolbetuximab did not result in any external or visceral foetal abnormalities (malformations or variations) (see section 5.3 of the SmPC).

The maternal and foetal NOAEL in the EFD study is 300 mg/kg, the highest dose administered. Wording on the lack of reproductive and developmental toxicity findings is included in section 4.6 and 5.3 of the SmPC.

Local tolerance observations were incorporated in the toxicology studies, which is acceptable. No unexpected findings were reported.

Since vomiting was observed in clinical studies and some cynomolgus monkeys treated with zolbetuximab, mechanistic studies were conducted to assess emetic potential using ferrets. In general, these studies are considered unnecessary, since vomiting as side effect is not surprising given the mechanism of action of zolbetuximab. However, the hypothesis was confirmed that zolbetuximab causes cellular damage to the gastric mucosa, resulting in retching and vomiting. Antiemetic medication somehow alleviated the symptoms, but a clear effect was not demonstrated since clinical signs and histopathology was very individual. Appropriate medication to reduce nausea and vomiting should be addressed in the clinic.

Tissue cross reactivity studies with zolbetuximab or murine surrogates were conducted with human, mouse or cynomolgus monkey tissue and confirmed restricted CLDN18.2 expression in the stomach. No findings of concern were noted.

The zolbetuximab drug product contains phosphoric acid as buffering agent/pH adjuster. The applicant sufficiently addressed the safety assessment of this compound.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, zolbetuximab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical data submitted as part of this application support a marketing authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Tabular overview of clinical studies

Study Number	**Study Name** (Patient number)	**Study Title**
[GM-IMAB-001] by Ganymed	FIM (n=15)	Clinical **First-in-human** Single-dose Escalation Study Evaluating the Safety and Tolerability of Claudiximab (iMAB-362) in Hospitalized Patients with Advanced Gastroesophageal Cancer
[GM-IMAB-001-04] by Ganymed	PILOT (n=28)	Multicenter, Open-label, Exploratory **Phase I** Pilot Study to Investigate Safety, Pharmacodynamics, and Pharmacokinetics of Immunological Effects and Activity of Combining Multiple Doses of IMAB362 with Immunomodulation (Zoledronic Acid, Interleukin-2) in Patients with Advanced Adenocarcinoma of the Stomach, the Lower Esophagus, or the Gastroesophageal Junction (PILOT)
[8951-CL-0104] by Astellas	NA (n=18)	A Phase 1 Open-label Study of Zolbetuximab (IMAB362) in Japanese Subjects with Locally Advanced or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
[8951-CL-0105] by Astellas	NA (n=12)	A Phase 1 Pharmacokinetic Study of Zolbetuximab (IMAB362) in Chinese Subjects with Locally Advanced Unresectable or Metastatic Gastric or Gastro-esophageal Junction (GEJ) Adenocarcinoma
[GM-IMAB-001-02] by Ganymed	MONO (n=54)	International, Multicenter, Open-label, **Phase II** Study to Investigate the Efficacy and Safety of Multiple Doses of IMAB362 in Patients with Advanced Adenocarcinoma of the Stomach or the Lower Esophagus
[GM-IMAB-001-03] by Ganymed	FAST (n=246)	A Randomized **Phase II** Multicenter, Open-label Study Evaluating the Efficacy and Safety of IMAB362 in Combination with the EOX (Epirubicin, Oxaliplatin, Capecitabine) Regimen as First-line Treatment of Patients with CLDN18.2-positive Advanced Adenocarcinomas of the Stomach, the Esophagus or the Gastroesophageal Junction (FAST)
[8951-CL-0103] by Astellas	ILUSTRO (n=54, ongoing)	A **Phase 2** Study of Zolbetuximab (IMAB362) as Monotherapy, in Combination with mFOLFOX6 and in Combination with Pembrolizumab in Subjects with Metastatic or Locally Advanced Unresectable Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma whose Tumors have High or Intermediate Claudin (CLDN) 18.2 Expression
[8951-CL-0301]	SPOTLIGHT	A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
[8951-CL-0302]	GLOW	A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX

		Compared with Placebo Plus CAPOX as First-line Treatment of Subjects with Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

CAPOX: capecitabine and oxaliplatin; CTD: common technical document; FIM: first-in-human; GEJ: gastroesophageal junction; HER2: human epidermal growth factor receptor 2; mFOLFOX6: modified 5-fluorouracil, leucovorin and oxaliplatin; NA: not applicable.

2.6.2. Clinical pharmacology

Zolbetuximab is a chimeric (mouse/human) IgG1 antibody directed against Claudin (CLDN) 18.2. CLDN18.2 is a tissue-specific cell surface molecule expressed in normal gastric tissue and in human cancers. It is an isoform of CLDN18, which is involved in the formation of tight junctions in epithelia and endothelia. Zolbetuximab binds selectively to cell lines transfected with CLDN18.2 or those that endogenously express CLDN18.2. It depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Zolbetuximab is a glycoprotein composed of 2 heavy chains (γ1-chains) consisting of 448 amino acid residues each and 2 light chains (κ-chains) consisting of 220 amino acid residues each.

One formulation was developed and used in all clinical pharmacology studies. It is a powder for reconstitution for intravenous (IV) infusion (100 mg zolbetuximab per vial, 20 mg/mL after reconstitution).

The proposed recommended dose of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy (mFOLFOX6, CAPOX) is a loading dose of 800 mg/m² IV in Cycle 1 on Day 1 followed by a maintenance dose of 600 mg/m² every 3 weeks (Q3W) or 400 mg/m² every 2 weeks (Q2W) until disease progression or unacceptable toxicity. The recommended dose is to be administered as IV infusion over a minimum of 2 h.

The clinical pharmacological program for zolbetuximab encompasses nine completed and ongoing clinical studies: four completed phase 1 studies, two completed phase 2 studies, one ongoing phase 2 study, and two ongoing Phase 3 studies.

Overall, four completed studies were conducted by Ganymed Pharmaceuticals AG:

- Phase 1 study **GM-IMAB-001 - FIM**
- Phase 2a study **GM-IMAB-001-02 - MONO**
- Phase 2 study **GM-IMAB-001-03 – FAST**
- Phase 1 study **GM-IMAB-001-04 – PILOT**.

A total of five completed and ongoing studies were initiated by Astellas:

- Phase 1 study **8951-CL-0104** (completed)
- Phase 1 study **8951-CL-0105** (completed)
- Phase 2 study **8951-CL-0103 - ILUSTRO** (ongoing)
- Phase 3 study **8951-CL-0301 – SPOTLIGHT** (ongoing)
- Phase 3 study **8951-CL-0302 – GLOW** (ongoing).

Zolbetuximab pharmacokinetic (PK) and immunogenicity profiles were evaluated in all clinical studies, except for PILOT, in which only the immunogenicity profile was evaluated. Single ascending doses of zolbetuximab were investigated in the first-in-human study GM-IMAB-001. Dose escalation in Japanese

patients was investigated in study 8951-CL-0104, and study 8951-CL-0105 was a PK and safety study in Chinese patients. Drug-drug interactions (DDI) were investigated in study ILUSTRO The effect of zolbetuximab on the QT interval corrected for heart rate (QTc) was analysed in studies ILUSTRO and 8951-CL-0104 and was analysed by modelling and simulation (Report: 8951-PK-0004, Date: 17-Dec-2021, Title: "Concentration-QTc Interval Modelling and Simulation of Zolbetuximab in Patients with Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma"). No dedicated thorough QT study was performed.

Efficacy and safety are being investigated in ongoing Phase 2 and Phase 3 studies in combination treatment with mFOLFOX6 (study SPOTLIGHT), CAPOX (study GLOW), and mFOLFOX6 ± nivolumab or with pembrolizumab or as single agent (study ILUSTRO). Furthermore, efficacy and safety were investigated in studies PILOT, MONO, and FAST. In study PILOT zolbetuximab was combined with an immunomodulation therapy (interleukin-2). In study FAST, a combination with EOX was investigated and in study MONO, zolbetuximab was tested as monotherapy.

Zolbetuximab has not been investigated in a dedicated renal or hepatic impairment study. No studies were conducted in healthy volunteers. Zolbetuximab has not been established in children and adolescents aged below 18 years. A waiver in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council has been granted.

The PK of zolbetuximab was investigated by non-compartmental analysis (NCA). In addition, population PK modelling and simulation was performed and are reported in Report: 8951-PK-0005, Date: 29-Mar-2023, Title: "Population Pharmacokinetic Analysis of Zolbetuximab in Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma".

The exposure-response (E-R) relationship for efficacy and safety was investigated by modelling and simulation (Report: 8951-PK-0006, Date: 27-Mar-2023, Title: "Exposure-Response Analyses of Zolbetuximab in Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma").

Moreover, a tumour dynamic analysis was also developed (Report: 8951-PK-0007, Date: 27-Mar-2023, Title: "Tumour Dynamics Modelling of Zolbetuximab in Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma").

2.6.2.1. Pharmacokinetics

Methods

- ***Analytical methods***

To determine serum concentration of zolbetuximab in human serum and to determine ADAs against Zolbetuximab in human serum two different bioanalytical methods each, enzyme-linked immunosorbent assay (ELISA) in the early clinical development program and electrochemiluminescence Immunoassay (ECLIA) in the later clinical development program, has been applied and evaluated in four different test facilities and were used for different studies during the clinical development program.

- ***Pharmacokinetic data analysis***

Blood samples for PK assessment were drawn at time-points as listed in Table 4. Serum PK of zolbetuximab was evaluated by standard non-compartmental analysis (NCA). PK data from studies Study GM-IMAB-001 (FIM), Study GM-IMAB-001-02 (MONO), Study 8951-CL-0104, Study 8951-CL-

0105, GM-IMAB-001-03 (FAST) and 8951-CL-0103 (ILUSTRO) were analysed with NCA. PK parameters evaluated include C_{max} C_{last}, C_{trough}, t_{max}, t_{last}, AUCs (AUC_{0-t}, AUC_{tau}, $AUC_{0-\infty}$, AUC_{last}, $AUC_{\%extra}$), CL and Vd, accumulation index (AI), $t_{1/2}$, as applicable. In addition, serum zolbetuximab samples from all studies, except study PILOT, were analysed by population PK modelling (report 8951-PK-0005). Primary as well as secondary PK parameters at different time-points were reported: C_{max}, C_{max_ss}, AUC, AUC_{ss} C_{trough}, C_{trough_ss}, C_{ave} (=AUC from start of treatment to 30 weeks/30 weeks). In addition, the duration of time above 30, 50 or 100 µg/mL ($T_{\geq 30}$, $T_{\geq 50}$ and $T_{\geq 100}$) at different time-points were reported.

Table 2: Sampling time points for blood sampling, LLOQ, tested doses and number of patients per study

Blood sampling time-points	Dosing	Number of patients
Study GM-IMAB-001 - FIM		
Pre-dose, end of infusion, 3, 8, 12, 24, 48, 96, 168, 336, 672 h after end of infusion LLOQ = 1 µg/mL	Zolbetuximab minimum 2 h IV infusion: 33, 100, 300, 600, 1000 mg/m² single doses	Total: n=15 3 per dose group
Study GM-IMAB-001-02 – MONO		
Week 1: pre-dose, end of infusion, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, 120, 336 h after end of infusion Week 3, 5, 7, 11: pre-dose Week 9: pre-dose, end of infusion, 1, 1.5, 2 h after end of infusion Week 13 - 19 or 15 - 39: Pre-dose, 4 h after end of infusion 7 - 9 weeks after last treatment 6 - 8 weeks after visit of 7 - 9 weeks after last treatment LLOQ = 1 µg/mL	<u>Cohort 1</u> Zolbetuximab 300 mg/m² Q2W 5 cycles <u>Cohorts 2 and 3</u> Zolbetuximab 600 mg/m² Q2W 5 cycles	Total: n=54 Cohort 1: n=4 Cohorts 2 and 3: n=50
Study GM-IMAB-001-03 – FAST		
Week 1: pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336 h after end of infusion Week 4 and 7: pre-dose Week 10: pre-dose, end of infusion, 0.5, 6, 24, 168, 336 hours after end of infusion Week 13, 16, 19, and 21: pre-dose 3 weeks after last EOX treatment LLOQ = 1 µg/mL	All Arms: epirubicin, oxaliplatin, capecitabine <u>Arm 2</u> Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m² Subsequent cycles: 600 mg/ m² Q3W <u>Arm 3</u> Zolbetuximab 2 to 3 h iv infusion: 1000 mg/m² Q3W	Total: n=246 Arm 1: n=84 Arm 2: n=77 Arm 3: n=85

Study 8951-CL-0104		
Cycle 1: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 3: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 5 and 9: Pre-dose, end of infusion Every 4 cycles ≥ Cycle 13: Pre-dose 30-day and 90-day follow-up visit LLOQ = 5 µg/mL	**Safety part** Arm A Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W Arm B Zolbetuximab minimum 2 h iv infusion: Day 1 1000 mg/ m^2 Q3W **Expansion part** Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W	Total: n=18 n=3 (Arm A) n=3 (Arm B) n=12 (Expansion)
Study 8951-CL-0105		
Cycle 1: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 3: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 5 and 9: Pre-dose, end of infusion Cycle 13 and 17: Pre-dose 30-day and 90-day follow-up visit LLOQ = 5 µg/mL	Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W	Total: n=12
Study 8951-CL-0103 - ILUSTRO		
Cohort 1A Cycle 1: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 3: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 5 and 9: Pre-dose, end of infusion Cycle 13 and 17: Pre-dose 30-day and 90-day follow-up visit Cohort 2	Cohorts 1A Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W Cohort 2	Planned: up to n=116 As of 28 Mar 2022 n=54: Cohort 1A: n=30 Cohort 2: n=21 Cohort 3A: n=3

Cycle 1 Day 3: Pre-dose, end of infusion, 0.5, 3, 6, 24, 120, 288, 456 h after end of infusion Cycle 2 Day 1: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 3, 5, 7, and 9: Pre-dose 30-day and 90-day follow-up visit <u>Cohort 3A</u> Cycle 1: Pre-dose, end of infusion, 0.5, 3, 6, 24, 72, 168, 336, 504 h after end of infusion Cycle 3, 5, and 9: Pre-dose, end of infusion Cycle 13 and 17: Pre-dose 30-day and 90-day follow-up visit LLOQ = 5 µg/mL	Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 3: 800 mg/m^2 (to enable mFOLFOX6 PK collection) Subsequent cycles: 600 mg/ m^2 Q3W mFOLFOX6 (max. 12 treatments over 4 cycles) <u>Cohort 3A</u> Zolbetuximab minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 (May be de-escalated to 600 mg/m² if DLTs are observed) Subsequent cycles: 600 mg/ m^2 Q3W Pembrolizumab: Day 1: 200 mg IV Q3W, 1 h after zolbetuximab infusion completed	
Study 8951-CL-0301 – SPOTLIGHT		
Cycle 1 Day 1: end of infusion Cycle 1 Day 22: pre-dose Cycle 2 Day 1: end of infusion Pre-dose on Day 1 of Cycles 3, 5, 7 and 9 30-day and 90-day follow-up visit LLOQ = 5 µg/mL	Zolbetuximab or Placebo minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W mFOLFOX6 (max. 12 treatments over 4 cycles)	Total: n=565 randomised
Study 8951-CL-0302 – GLOW		
Cycle 1 Day 1: end of infusion Cycle 2 Day 1: pre-dose Cycle 3 Day 1: end of infusion Pre-dose on Day 1 of Cycles 5, 9, 13 and 17 30-day and 90-day follow-up visit LLOQ = 5 µg/mL	Zolbetuximab or Placebo minimum 2 h iv infusion: Loading dose Cycle 1 Day 1: 800 mg/m^2 Subsequent cycles: 600 mg/ m^2 Q3W CAPOX (total of 8 cycles; 21 days/cycle)	Total: n=507 randomised

- ***Evaluation and qualification of models***

Population PK model selection was done based on precision and plausibility of parameter estimates and graphical model evaluation (e.g. goodness-of-fit [GOF] plots). Nonparametric bootstrap analysis and prediction-corrected visual predictive check (pcVPC) were carried out using the final model (1000 bootstrap replicates and 500 simulations, respectively).

- ***Statistical methods***

Generally, standard summary statistics like means, standard deviation (SD), median, percentiles, minimum (min), maximum (max), % coefficient of variation (%CV), geometric mean (GM) and geometric %CV (Geo %CV) have been used. For comparison (e.g. of GMR) the 90 % confidence intervals (CI) were calculated. PK parameters were calculated by Phoenix WinNonlin® software version 6.4 or higher. Statistical assessments of dose proportionality were conducted by R.

Absorption

Zolbetuximab is used as IV infusion. Therefore, the bioavailability is 100 %. No absorption studies have been conducted.

Only one formulation was developed and used in all clinical pharmacology studies. The to-be-market formulation is a powder for reconstitution for IV infusion (100 mg zolbetuximab per vial, 20 mg/mL after reconstitution).

No food effect studies have been conducted.

Distribution

- **Non-compartmental analysis**

In **Study GM-IMAB-001** the observed mean Vz ranged from 6.56 L to 8.90 L in the 33-1000 mg/m² dose range.

In Study **GM-IMAB-001-02 (MONO)** the observed mean Vz was 3.77 L and 4.61 L in the 300 mg/m² and 600 mg/m² dose respectively.

In Study **8951-CL-0104** the observed mean Vz was 5.84 L in the 800/600mg/m² dose.

In Study **8951-CL-0105** the observed mean Vz was 5.60 L in the 800/600mg/m² dose.

In study **GM-IMAB-001-03 (FAST)** the observed mean Vz was 8.742 L in the 800/600mg/m² dose.

In Study **8951-CL-0103 (ILUSTRO)** the observed mean Vz was 6.25 L in the 800/600mg/m² dose

- **Population PK analysis**

Based on an updated population PK analysis the typical overall volume of distribution (V) is 5.53 L with 3.04 L (20.1 %CV) L for the central compartment (V1) and 2.49L (27.4 %CV) for the peripheral compartment (V2).

BSA was identified as statistically significant covariate on V1 and V2 with an estimated factor of 0.97. Volumes of distribution increased with increasing BSA compared to a population typical BSA of 1.7 m².

Combination chemotherapy with EOX was identified to have an statistically significant effect on V1 (estimate of 0.466 with RSE of 11.7%). EOX was not administered in Phase III studies.

The proposed recommended doses are based on BSA. No dose adjustments are proposed based on EOX combination therapy.

Elimination

- **Non-compartmental analysis**

In **Study GM-IMAB-001 (FIM)** the observed mean CL ranged from 0.290 L/day to 0.609 L/day and the mean t1/2 ranged from 13.1 day to 21.7 day.

In Study **GM-IMAB-001-02 (MONO)** the observed mean CL ranged from 0.496 L/day to 0.718 L/day and the mean t1/2 was 5.38 to 5.83 days (300mg/m² and 600mg/m² dosing regimen).

In Study **8951-CL-0104** the observed mean CL was 0.506 L/day and the mean t1/2 was 8.82 days (800/600mg/m² dosing regimen).

In Study **8951-CL-0105** the observed mean CL was 0.624 L/day and the mean t1/2 was 7.87 days (800/600mg/m² dosing regimen).

In study **GM-IMAB-001-03 (FAST)** the observed mean CL was 0.662 L/day and the mean t1/2 was 10.69 days (800/600mg/m² dosing regimen).

In Study **8951-CL-0103 (ILUSTRO)** the observed mean CL was 0.593 L/day and the mean t1/2 was 8.72 days (800/600mg/m² dosing regimen)

- **Population PK analysis**

Based on an updated population PK analysis the typical systemic zolbetuximab clearance (CLss) at steady state was estimated to 0.0117 L/h (26 %CV), with a time-dependent component.

BSA was identified as statistically significant covariate on systemic clearance at steady state, time-dependent CL (CL_T) and inter-compartmental clearance (Q) with an estimated factor of 1.06. Clearances increased with increasing BSA compared to a population typical BSA of 1.7 m².

Sex was identified as a statistically significant effect on CLss of zolbetuximab (estimate = -0.195 (RSE=14%). Compared to male participants, zolbetuximab CLss in female participants was 19.5% lower (CL=0.01 L/h).

Serum albumin (baseline) was identified as a statistically significant covariate on CLss (estimate = -0.535 with RSE = 23.2 %). CLss decreased with increasing albumin compared to the population typical serum albumin of 39.1 g/L.

Prior gastrectomy status (if gastrectomy) was identified as a statistically significant covariate on CLss (estimate = -0.182 with RSE = 14.2%) and mainly on CL_T (estimate = -0.495 with RSE = 8 %). Compared to participants without prior gastrectomy, zolbetuximab CL of participants with prior gastrectomy ís expected to be lower.

The elimination half-life of zolbetuximab ranged from 7.6 to 15.2 days.

The proposed recommended doses are based on BSA. No dose adjustments are proposed based on sex, albumin levels and prior gastrectomy status.

The final former and updated pop PK model structure and estimates are presented in the table below.

Table 3: Former and currently updated pop PK model

Parameter [Unit]	Original Model	Parameter [Unit]	Revised Model
OFV	**43292.192**	**OFV**	**42561.715**
CL [L/h]	0.0150 (3.3%)	CL_{SS} [L/h]	0.0117 (2.6%)
		CL_T [L/h]	0.0159 (4.7%)
		K_{decay} [1/day]	0.0209 (5.6%)
V1 [L]	3.18 (1.1%)	V1 [L]	3.04 (1.5%)
Q [L/h]	0.0271 (3.0%)	Q [L/h]	0.0235 (7.6%)
V2 [L]	13.2 (5.6%)	V2 [L]	2.49 (4.2%)
Covariate Effects (%RSE)		**Covariate Effects (%RSE)**	
BSA on CL, Q	1.19 (11.8%)	BSA on CL_{SS}, CL_T, Q	1.06 (10.8%)
BSA on V1, V2	1.13 (7.3%)	BSA on V1, V2	0.968 (8.8%)
ALB on CL	-0.891 (14.0%)	ALB on CL_{SS}	-0.535 (23.2%)
GAST on CL (if gastrectomy)	-0.220 (14.7%)	GAST on CL_{SS} (if gastrectomy)	-0.182 (14.2%)
SEX on CL (if female)	-0.198 (19.5%)	SEX on CL_{SS} (if female)	-0.195 (14.0%)
GAST on V2 (if gastrectomy)	-0.528 (8.3%)	GAST on CLT (if gastrectomy)	-0.495 (8.0%)
		ALB on K_{decay}	1.48 (26.0%)
		GAST on V1 (if gastrectomy)	0.103 (23.0%)
		HGB on V1	-0.374 (16.8%)
		TBILI on V1	0.0347 (39.8%)
		SEX on V1 (if female)	-0.108 (18.7%)
		COMB on V1 (if EOX)	0.466 (11.7%)
Inter-individual variability [shrinkage]		**Inter-individual variability [shrinkage]**	
ω_{CL} [CV%]	39.6% [21.7%]	ω_{CLSS} [CV%]	26.3% [34.8%]
		ω_{CLT} [CV%]	76.1% [26.7%]
		ω_{Kdecay} [CV%]	77.3% [40.3%]
ω_{V1} [CV%]	25.8% [12.3%]	ω_{V1} [CV%]	20.1% [16.7%]
		ω_{Q} [CV%]	63.9% [63.4%]
ω_{V2} [CV%]	97.6% [25.1%]	ω_{V2} [CV%]	27.4% [72.0%]
Residual variability (%RSE)		**Residual variability (%RSE)**	
Proportional error [CV%]	0.170 (1.8%)	Proportional error [CV%]	0.169 (0.6%)
Additive error [µg/mL]	8.46 (6.5%)	Additive error [µg/mL]	4.03 (4.5%)

ALB: albumin; BSA: body surface area; CL: systemic clearance; CL_{SS}: systemic clearance at steady state; CL_T; time-dependently decaying systemic clearance; COMB: combination chemotherapy; CV%: coefficient of variance; EOX: epirubicin, oxaliplatin, capecitabine; GAST: gastrectomy status; HGB: hemoglobin; K_{decay}: first-order decay constant describing the rate of decrease of CL_T; OFV: objective function value; PK: pharmacokinetic; Q: inter-compartmental clearance; RSE: relative standard error; TBILI: total bilirubin; V1: volume of distribution of the central compartment; V2: volume of distribution of the peripheral compartment; ω: inter-individual variability.

Metabolism

Zolbetuximab is expected to be catabolised into small peptides and amino acids. No metabolism studies have been conducted.

Dose proportionality and time dependencies

The mean Cmax values after a single administration of Zolbetuximab were approximately dose proportional from 33 mg/m² to 1000 mg/m² [Study FIM]. The increase in zolbetuximab exposure was approximately dose-proportional between 800/600 mg/m² and 1000 mg/m² dose regimens in both cycle 1 (single dose) and cycle 4 (multiple doses) [Study FAST].

The observed mean accumulation ratio for Cmax and AUC in study ILUSTRO, study 8951-CL-0105, study 8951-CL-0104 and study FAST is presented in the table below.

Table 4: Accumulation Ratios in Zolbetuximab Clinical Studies (Observed Data)

STUDY (800/600 mg/m² Q3W)		R_{ac} (AUC_{21d})			R_{ac} (C_{max})		
		N	Mean	SD	N	Mean	SD
ILUSTRO 8951-CL-0103	Cohort 1A	11	1.09	0.368	11	0.824	0.106
	Cohort 2	12	1.31	0.428	16	0.790	0.137
8951-CL-0104		7	0.84	0.235	10	0.886	0.147
8951-CL-0105		2	1.71	NA	2	1.17	NA
FAST (GM-IMAB-001-03)		3	1.49	0.055	18	0.995	0.179
Total		**35**	**1.19**	**0.408**	**57**	**0.892**	**0.175**

AUC_{21d}: area under the concentration-time curve from the time of dosing to day 21 postdosing; C_{max}: maximum concentration; NA: not applicable; Q3W: every 3 weeks; $R_{ac}(AUC_{21d})$: accumulation ratio calculated using AUC_{21d}; $R_{ac}(C_{max})$: accumulation ratio calculated using C_{max}.

Calculation was done by using: cycle 3 vs cycle 1 data in ILUSTRO Cohort 1A, 8951-CL-0104 and 8951-CL-0105; cycle 2 vs cycle 1 data in ILUSTRO Cohort 2; cycle 4 vs cycle 1 data in FAST Arm 2.

Source: NCA_RACresult.R

The revised model indicates a higher drug accumulation than the original model. Following 800/600 mg/m2 Q3W treatment, steady state was achieved by 24 weeks in the revised model with a mean (SD) Cmax and AUCtau of 453 (82) µg/mL and 4125 (1169) day•µg/mL, respectively. Taking the loading dose into account, the simulations showed an average accumulation of 1.96 for zolbetuximab AUC21d, while no accumulation is expected for Cmax. Despite the small differences in the concentration-time profiles, the original model and the revised model have a high level of consistency in the estimations of Cave and Cmax_1st.

Intra-and inter-individual variability

- **Non-compartmental analysis**

Study GM-IMAB-001 (FIM)

In Study GM-IMAB-001 (FIM), low to high inter-subject variability was observed. Geometric %CV (% geometric coefficient of variation of PK parameters) for AUC parameters (AUCinf) was within levels of 25.0% to 85.5% and geometric mean %CV of Cmax was within levels of 1.8% to 31.5%.

Study GM-IMAB-001-02 (MONO)

In Study GM-IMAB-001-02 (Mono), inter-subject variability (Geo%CV) of AUC0-14d, AUCinf and Cmax after first dose (Cycle 1 day1) ranged from 10.9% to 30%, 23.9% to 48.1% and 18.6% to 25.2%, respectively. After multiple dosing, inter-subject variability (%CV) of Ctrough ranged between 32.2% to 64%.

Study 8951-CL-0103 (ILUSTRO)

In Study 8951-CL-0103 (ILUSTRO) Cohort 1A, inter-subject variability (Geo%CV) of AUCtau and Cmax after first dose (Cycle 1 day1) was 36.2% (%CV:38.0%) and 28.9% (%CV:30.2%), respectively. After C3D1, inter-subject variability (Geo%CV) for AUCtau was 47.6% (%CV:48.1%) and for Cmax 22.9% (%CV:21.9%). After multiple dosing, inter-subject variability (%CV) of Ctrough ranged between 29.9 % to 79.8%.

Cohort 2: inter-subject variability (Geo%CV) of AUCtau and Cmax after first dose (Cycle 1 day3) was 39.2 (%CV:39.3%) and 17.9% (%CV:17.3%), respectively. After C2D1, inter-subject variability (GeoMean%CV) for AUCtau was 44.5% (%CV:42.2%) and for Cmax 13.8% (%CV:13.7%). After multiple dosing, inter-subject variability (%CV) of Ctrough ranged between 51.0 % to 130.1%.

Cohort 3A: inter-subject variability (Geo%CV) of AUCtau and Cmax after first dose (Cycle 1 day1) was 24.3 (%CV:22.3%) and 22.4% (%CV:20.5%), respectively.

Study 8951-CL-0104

In Study 8951-CL-0104, inter-subject variability (Geo%CV) of AUCtau and Cmax after first dose (Cycle 1 day1) ranged from 12.4% to 35.6% (%CV:12.6%-31.0%) and 10.5%-22.4% (%CV:10.8%-21.9%), respectively. After C3D1, inter-subject variability (Geo%CV) for AUCtau was 54.4% (%CV:48.2%) and for Cmax 22.8% (%CV:19.4%).

Study 8951-CL-0105

In Study 8951-CL-0105, inter-subject variability (Geo%CV) of AUCtau and Cmax after first dose (Cycle 1 day1) was 24.3% (%CV:24.5%) and 16.7% (%CV:16.4%), respectively. After C3D1, inter-subject variability (GeoMean%CV) was not applicable for AUCtau and for Cmax.

Study GM-IMAB-001-03 (FAST)

In Study GM-IMAB-001-03 (FAST), inter-subject variability (Geo%CV) of AUC0-21d and Cmax after first dose (Cycle 1) ranged from 36.9% to 47.5% (%CV: 28.1%-32.5%) and 21.2% to 31.0% (%CV: 18.7%-25.7%), respectively. At Cycle 4, inter-subject variability of AUC0-21d and Cmax ranged between 25.2% to 37.6% (%CV:21.2-26.5%) and 20.3% to 20.5% (%CV:19.1%-19.6%). After multiple dosing, inter-subject variability (%CV) of Ctrough ranged between 29.6 % to 82.1%.

Study 8951-CL-0301 (SPOTLIGHT)

In Study 8951-CL-301 (SPOTLIGHT), inter-subject variability (%CV) of Ctrough after multiple dosing ranged from 41.8%-90.8%.

Study 8951-CL-0302 (GLOW)

In Study 8951-CL-302 (GLOW), inter-subject variability (%CV) of Ctrough after multiple dosing ranged from 46.6%-81.1%.

- **Population PK analysis**

Based on an updated population PK analysis, interindividual variability (IIV) in CLss, CLT, Kdecay (first-order decay constant describing the rate of decrease of CLT), V1, Q and V2 were 26.3, 76.1, 77.3, 20.1, 63.9 and 27.4 %CV, respectively. C_{max}, AUC_{21d}, C_{trough}, C_{ave} for the 1st 42 days and at steady state at 42 days for the Q3W (800 mg/m² followed by 600 mg/m²) and Q2W (800 mg/m² followed by 400 mg/m²) regimen are listed in Table 7 and Table 8 (updated pop PK model).

Table 5: Selected model-based zolbetuximab exposures after dosing of 800 mg/m² followed by 600 mg/m² Q3W or 400 mg/m² Q2W – report 8951-PK-0005 (former model)

Exposure mean (min-max), median	**1st 42 days[1]** Day 1 800 mg/m² Day 21 600 mg/m²	**1st 42 days[2]** simulated Day 1 800 mg/m² Day 14 400 mg/m² Day 28 400 mg/m²	**Steady-state at 42 days[3]** Day 21 600 mg/m² Day 42 600 mg/m²	**Steady-state at 42 days[4]** simulated Day 14 400 mg/m² Day 28 400 mg/m² Day 42 400 mg/m²	

C_{max} [µg/mL]	434 (171-1117) 425	434 (171-1117) 425	425 (144-902) 416	326 (104-639) 318	
AUC_{21d} [day*µg/mL]	2263 (788-6102) 2106	2520 (887-6711) 2349	3340 (892-9527) 3131	3349 (892-9598) 3140	
C_{trough} [µg/mL]	61 (9-237.6) 53.3	73.8 (11.5-285.2) 64.4	101 (14-390) 92	110 (18-408) 99	
C_{ave} [µg/mL]	140 (40-392) 131	143 (41-400) 135	140 (40-392) 131	143 (41-400) 135	
[1]1st 42 days: 1st dose of 800 mg/m² on day 1 + 1st dose of 600 mg/m² on day 21, measurement day 42 pre-dose [2]1st 42 days: 1st dose of 800 mg/m² on day 1 + 1st dose of 400 mg/m² on day 14 + 2nd dose of 400 mg/m² on day 28, measurement day 42 pre-dose [3]Steady-state at 42 days: after two dose of 600 mg/m² (on day 168 and 189), measurement day 210 pre-dose [4]Steady-state at 42 days: after three dose of 400 mg/m² (on day 168, 182, and 196), measurement day 210 pre-dose AUC_{21d}: AUC from the time of dosing to 21 days, calculated as half of AUC from the time of dosing to 42 days C_{ave}: average concentration throughout the treatment d					

Model predicted exposure after model update (time-dependencies in CL):

Table 6: Model-estimated Exposure Metrics of Zolbetuximab at 800/600 mg/m2 Q3W (Revised Model)

Mean (SD) Median (Min – Max)	**First dose (800 mg/m²)**	**Steady State (600 mg/m²)**	**Accumulation Ratio**
C_{max} (µg /mL)	454 (87) 442 (251 – 1031)	453 (82) 441 (256 – 842)	1.006 (0.119) 0.987 (0.795 – 1.672)
AUC_{21d} (day•µg/mL)	2176 (606) 2104 (633 – 4602)	4125 (1169) 3945 (1555 – 10421)	1.960 (0.530) 1.850 (1.040 – 5.880)
C_{trough} (µg/mL)	36.8 (23.2) 30.6 (2.3 – 148)	114 (50) 104 (23 – 405)	-
C_{ave} (µg/mL)	158 (48) 151 (56 – 396)		-

AUC_{21d}: area under the concentration-time curve from the time of dosing to day 21 postdosing; C_{ave}: average concentration throughout the treatment; C_{max}: maximum concentration; C_{trough}: trough concentration; Max: maximum, Min: minimum; Q3W: every 3 weeks.
For first dose, simulation was done for a 3-week interval after the first dose.
For steady state, simulation was done for a 3-week interval from week 28 to week 31.

Pharmacokinetics in target population

- **Non-compartmental analysis**

To date, 9 clinical studies of zolbetuximab have been completed or are ongoing in adult patients with advanced adenocarcinoma of the stomach, oesophagus or GEJ whose tumours are CLDN18.2-positive. Zolbetuximab PK profiles were evaluated by NCA in 6 of these studies. A summary of the key results of all these 6 studies is provided in the table below.

Table 7: Summary of Zolbetuximab Pharmacokinetic Studies with Key Results

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route	Parameters of Investigational Drug		
Zolbetuximab used as monotherapy						
GM-IMAB-001 (FIM)	Phase 1, multicenter, non-randomized, inter-patient single-dose escalation, open-label study with a single intravenous infusion of zolbetuximab n = 15	Participants with advanced gastroesophageal cancer§ 11 M/4 F participants 61.3 (46, 76)	Zolbetuximab Single dose administration	C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{inf}, day•µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			33 mg/m²	15.1 (1.8) 15.1 (1.8) n = 3	165 (24.6) 162 (25.0) n = 3	0.0826 (0.0792-0.201) n = 3
			100 mg/m²	58.7 (29.5) 56.9 (31.5) n = 3	697 (38.1) 666 (36.6) n = 3	0.106 (0.101-0.418) n = 3
			300 mg/m²	170 (3.5) 170 (3.5) n = 3	2500 (50.6) 2240 (66.6) n = 3	0.125 (0.0833-0.208) n = 3
			600 mg/m²	331 (11.1) 329 (11.4) n = 3	2760 (69.0) 2320 (85.5) n = 3	0.211 (0.0833-1.10) n = 3
			1000 mg/m²	517 (14.9) 514 (14.5) n = 3	5080 (27.8) 4960 (26.7) n = 3	0.208 (0.0979-0.232) n = 3
GM-IMAB-001-02 (MONO)	Phase 2a multicenter, international, open-label, interventional multiple-dose clinical study n = 54 (FAS) n = 44 (PKAS)	Participants with metastatic, refractory or recurrent advanced adenocarcinoma of the stomach or lower esophagus§ 37 M/17 F participants	**Cohort 1 (Zolbetuximab 300 mg/m² Q2W)**			
				C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{14d}, day·µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			Zolbetuximab 300 mg/m²	288 (23.8) 282 (25.2) n = 4	776 (10.7) 773 (10.9) n = 4	0.205 (0.153, 0.378) n = 4

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route		Parameters of Investigational Drug		
		59.1 (35, 77) years	**Cohort 2 + 3 (Zolbetuximab 600 mg/m² Q2W)**				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{14d}, day·µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			Zolbetuximab 600 mg/m²		355 (19.5) 349 (18.6) n = 40	1450 (28.2) 1390 (30.0) n = 38	0.148 (0.0833, 0.340) n = 40
8951-CL-0103 (ILUSTRO) (Cohort 1A)	Phase 2, open-label, multi-arm, non-randomized, multicenter n = 54 (PKAS): Cohort 1A: n = 30	Patients with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive§ Cohort 1A: 20M/10F patients 56.50 (32, 79) years	**Cohort 1A (Zolbetuximab single agent 800/600 mg/m2 Q3W)**				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{tau}, day•µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			Zolbetuximab 800 mg/m²	C1D1	448 (30.2) 430 (28.9) n = 23	2210 (38.0) 2080 (36.2) n = 23	0.174 0.0889 – 0.355 n = 23
			Zolbetuximab 600 mg/m²	C3D1	362 (21.9) 354 (22.9) n = 12	2740 (48.1) 2490 (47.6) n = 11	0.120 0.0868 – 0.247 n = 12
8951-CL-0104	Phase 1, open-label study of zolbetuximab in 2 parts: (1) Safety Part; (2) Expansion Part n = 18 (PKAS) Arm A: n = 3 Arm B: n = 3 Expansion Part: n = 12	Japanese participants with locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive§ Arm A: 2M/3F Arm B: 0M/3F Extension Part: 5M/7F Arm A: 57.7 (49, 65) years Arm B: 59.3 (49, 65) years Extension Part: 61.7 (46, 82) years	**Arm A (Zolbetuximab 800/600 mg/m² Q3W)**				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{tau}, day•µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			Zolbetuximab 800 mg/m²	C1D1	378 (10.8) 377 (10.5) n = 3	2300 (31.0) 2220 (35.6) n = 3	0.211 (0.194, 0.248) n = 3
			Zolbetuximab 600 mg/m²	C3D1	344 (31.2) 331 (36.5) n = 3	2190 (NA) NA (NA) n = 2	0.251 (0.247, 0.284) n = 3
			Arm B (Zolbetuximab 1000 mg/m² from C1D1 Q3W)				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	AUC_{tau}, day•µg/mL Mean (%CV) GeoMean, (%CV) n	t_{max}, day Median (min, max) n
			Zolbetuximab 1000 mg/m²	C1D1	805 (20.7) 792 (22.4) n = 3	2360 (12.6) 2350 (12.4) n = 3	0.292 (0.203, 0.294) n = 3

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route		Parameters of Investigational Drug		
			Zolbetuximab 1000 mg/m²	C3D1	800 (NA) NA (NA) n = 1	NA (NA) NA (NA) n = 0	0.266 (0.266, 0.266) n = 1
			Expansion Part (Zolbetuximab 800/600 mg/m² Q3W)				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	**AUC_{tau}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
			Zolbetuximab 800 mg/m²	C1D1	508 (21.9) 498 (21.2) n = 12	2420 (27.0) 2340 (27.1) n = 10	0.223 (0.138, 0.349) n = 12
			Zolbetuximab 600 mg/m²	C3D1	411 (13.8) 408 (13.9) n = 7	2080 (45.1) 1910 (49.2) n = 5	0.224 (0.106, 0.269) n = 7
			Total: Zolbetuximab 800/600 mg/m² (Arm A + Expansion Part)				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	**AUC_{tau}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
			Zolbetuximab 800 mg/m²	C1D1	482 (23.5) 471 (22.5) n = 15	2390 (26.7) 2310 (27.7) n = 13	0.211 (0.138, 0.349) n = 15
			Zolbetuximab 600 mg/m²	C3D1	391 (19.4) 383 (22.8) n = 10	2110 (48.2) 1890 (54.4) n = 7	0.236 (0.106, 0.284) n = 10
8951-CL-0105	Phase 1, open-label PK and safety study of zolbetuximab n = 12 (PKAS)	Chinese participants with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive§ 6M/6F patients 53.4 (31, 69) years			**C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n**	**AUC_{tau}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
			Zolbetuximab 800 mg/m²	C1D1	372 (16.4) 367 (16.7) n = 12	2280 (24.5) 2220 (24.3) n = 7	0.220 (0.142, 0.347) n = 12
			Zolbetuximab 600 mg/m²	C3D1	422 (NA) NA (NA) n = 2	4700 (NA) NA (NA) n = 2	0.742 (0.347, 1.14) n = 2

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route		Parameters of Investigational Drug		
Zolbetuximab used in combination with chemotherapy or pembrolizumab							
GM-IMAB-001-03 (FAST)	Phase 2, multinational, multicenter, open-label, randomized study n = 246 (FAS) Arm 1 (EOX alone): n = 84 Arm 2: n = 77 Arm 3: n = 85	Patients with advanced adenocarcinomas of the stomach, the esophagus or GEJ whose tumors are CLDN18.2-positive§ Arm 1: 56M/28F Arm 2: 47M/30F Arm 3: 57M/28F Arm 1: 55.7 (24, 73) years Arm 2: 57.0 (22, 77) years Arm 3: 57.2 (28, 70)	**Zolbetuximab + EOX**				
			Zolbetuximab Arm 2: 800 mg/m² Arm 3: 1000 mg/m²	Cycle 1	**C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n**	**AUC_{21day}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
					Arm 2 (Zolbetuximab 800/600 mg/m² + EOX Q3W)		
					328 (18.7) 322 (21.2) n = 22	1990 (28.1) 1910 (36.9) n = 21	0.104 (0.083, 1.1) n = 22
					Arm 3 (Zolbetuximab 1000 mg/m² + EOX Q3W)		
					431 (25.7) 416 (31.0) n = 27	2620 (32.5) 2460 (47.5) n = 25	0.129 (0.083, 0.417) n = 27
			Zolbetuximab Arm 2: 600 mg/m² Arm 3: 1000 mg/m²	Cycle 4	**Arm 2 (Zolbetuximab 800/600 mg/m² + EOX Q3W)**		
					319 (19.1) 314 (20.5) n = 18	3340 (21.2) 3290 (25.2) n = 3	0.092 (0.083, 0.208) n = 18
					Arm 3 (Zolbetuximab 1000 mg/m² + EOX Q3W)		
					555 (19.6) 545 (20.3) n = 22	4800 (26.5) 4600 (37.6) n = 21	0.167 (0.083, 0.385) n = 22
8951-CL-0103 (ILUSTRO) (Cohort 2 and 3A)	Phase 2, open-label, multi-arm, non-randomized, multicenter n = 54 (PKAS): Cohort 2: n = 21 Cohort 3A: n = 3	Patients with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive§ Cohort 2: 12M/9F patients 58.86 (36, 74) years Cohort 3A: 1M/2F patients 65.67 (58, 74) years	**Cohort 2 (Zolbetuximab 800/600 mg/m² + mFOLFOX6 Q3W)**				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	**AUC_{tau}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
			Zolbetuximab 800 mg/m²	C1D3	477 (17.3) 470 (17.9) n = 16	1900 (39.3) 1770 (39.2) n = 15	0.150 0.0382 – 0.292 n = 18
			Zolbetuximab 600 mg/m²	C2D1	369 (13.7) 365 (13.8) n = 17	2400 (42.2) 2210 (44.5) n = 14	0.183 0.106 – 0.872 n = 18
			Cohort 3A (Zolbetuximab 800/600 mg/m² + pembrolizumab Q3W)				
					C_{max}, µg/mL Mean (%CV) GeoMean, (%CV) n	**AUC_{tau}, day·µg/mL Mean (%CV) GeoMean, (%CV) n**	**t_{max}, day Median (min, max) n**
			Zolbetuximab 800 mg/m²	C1D1	433 (20.5) 426 (22.4) n = 3	2930 (22.3) 2870 (24.3) n = 3	0.160 (0.151, 0.186) n = 3

Data cutoffs: 31 Jan 2019 (FAST); 03 May 2021 (ILUSTRO)

All participants who received at least 1 dose of study drug and for whom at least 1 pharmacokinetic measurement upon treatment was available (Pharmacokinetic Analysis Set).

C: cycle; CLDN18.2: claudin-18 splice variant 2; CV: coefficient of variation; D: day; EOX: epirubicin, oxaliplatin and capecitabine; F: female; FAS: full analysis set; GEJ: gastroesophageal junction; GeoMean: geometric mean; M: male; max: maximum; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; min: minimum; PKAS: Pharmacokinetics Analysis Set; Q2W: every 2 weeks; Q3W: every 3 weeks.

§ CLDN18.2 status is defined in [Table 1]

Source: [Study 8951-CL-0103 (ILUSTRO), Table 8, Table 35, Table 36]; [Study 8951-CL-0104 Table 7, Table 22, Table 23]; [Study 8951-CL-0105 Table 3, Table 16]; [Study gm-imab-001-02 MONO Trial, Table 4, Table 8]; [Study gm-imab-001-03 FAST Trial, Table 3, Table 30]; [Study gm-imab-001-clr-en-final-02 FIM Trial, Table 3]; [PK Report Amendment for Study GM-IMAB-001, Table 4].

Study 8951-CL-0301 (SPOTLIGHT)

Study 8951-CL-0301 (SPOTLIGHT) is a global, multicenter, double-blind, 1:1 randomized, phase 3 study to evaluate the efficacy of zolbetuximab plus mFOLFOX6 vs placebo plus mFOLFOX6 as first-line treatment in participants with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive.

Participants received either zolbetuximab (Arm A) or placebo (Arm B) on days 1 and 22 in each cycle (each cycle is approximately 6 weeks [42-day]) starting on cycle 1 day 1 until the participants met study treatment discontinuation criteria. Zolbetuximab was given as 800/600 mg/m² Q3W as a minimum 2 h

infusion. Participants in both arms also received mFOLFOX6 on days 1, 15 and 29 in each 42-day cycle for up to 12 treatments over 4 or more cycles and might continue to receive 5-FU and folinic acid at the investigator's discretion.

Blood samples for the determination of zolbetuximab serum concentrations were collected at predose on cycle 1 day 22 and day 1 of cycles 3, 5, 7 and 9, at EOI of cycle 1 day 1 and cycle 2 day 1, and at 30-day and 90-day safety follow-up visits of zolbetuximab. The summary of sparse serum concentrations of zolbetuximab are presented.

Table 8: Individual and Summary of Serum Concentrations (µg/mL) of Zolbetuximab (PKAS)

Statistics	C1D1 EOI	C1D22 Pre dose	C2D1 EOI	C3D1 Pre dose	C5D1 Pre dose	C7D1 Pre dose	C9D1 Predose	30 D SFU	90 D FU
N	219	181	197	184	139	97	58	85	74
Mean (SD)	451 (142)	40.9 (37.2)	368 (132)	70.1 (49.8)	97.4 (50.8)	118 (64.9)	135 (56.2)	54.5 (42.3)	10.1 (12.7)
%CV	31.5	90.8	35.9	71.0	52.1	55.0	41.8	77.6	125.7
Median (min, max)	452 (0, 1580)	30.4 (0, 326)	373 (12.0, 950)	61.1 (0, 256)	91.9 (0, 224)	104 (0, 378)	128 (48.0, 251)	44.5 (0, 176)	6.55 (0, 43.2)

Data cutoff: 09 Sep 2022

Concentrations below the lower limit of quantification (5 µg/mL) were set to zero.

EOI: end of infusion; C: cycle; D: day; 30 D SFU: 30 day safety follow-up visit – zolbetuximab; 90 D FU: 90 day follow up visit – zolbetuximab; Max: maximum; Min: minimum; PKAS: pharmacokinetic analysis set.

Source: End-of-Text Table 9.4.1

Study 8951-CL-0302 (GLOW)

Study 8951-CL-0302 (GLOW) is a global, multicenter, double-blind, 1:1 randomized, phase 3 study to evaluate the efficacy of zolbetuximab plus CAPOX vs placebo plus CAPOX as first-line treatment in participants with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive.

Participants received either zolbetuximab (Arm A) or placebo (Arm B) on day 1 of each cycle (each cycle is approximately 3 weeks [21-day]) starting on cycle 1 until the participants met study treatment discontinuation criteria. Zolbetuximab was given as 800/600 mg/m² Q3W as a minimum 2 h infusion. Participants in both arms also received CAPOX for 8 cycles (oxaliplatin on day 1 of each cycle; capecitabine twice daily on days 1 through 14 of each cycle) and might continue to receive capecitabine at the investigator's discretion.

Blood samples for the determination of zolbetuximab serum concentrations were collected at predose on day 1 of cycles 2, 5, 9, 13 and 17, at EOI of cycle 1 day 1 and cycle 3 day 1, and at 30-day and 90-day safety follow-up visits of zolbetuximab.

Table 9: Summary of Serum Concentration (µg/mL) of Zolbetuximab (Pharmacokinetic Analysis Set)

Statistics	C1D1 EOI	C2D1 Pre-dose	C3D1 EOI	C5D1 Pre-dose	C9D1 Pre-dose	C13D1 Pre-dose	C17D1 Pre-dose	30D SFU	90D FU
N	223	217	185	160	92	52	37	65	47
Mean (SD)	464 (136)	38.6 (31.3)	382 (133)	74.1 (51.6)	99.6 (58.2)	119 (55.6)	147 (70.5)	53.1 (48.5)	9.06 (11.0)
%CV	29.4	81.1	34.7	69.7	58.4	46.6	47.9	91.3	121.2
Median (min, max)	451 (0, 829)	30.2 (0, 153)	389 (0, 691)	63.4 (0, 302)	90.9 (0, 322)	117 (26.8, 252)	138 (23.3, 342)	48.6 (0, 184)	6.13 (0, 44.2)

Data cutoff: 07 Oct 2022

30D SFU: 30-day safety follow-up visit - zolbetuximab; 90D FU: 90 day follow up visit – zolbetuximab; C: cycle; CV: coefficient of variation; D: day; EOI: end of infusion; max: maximum; min: minimum; SD: standard deviation

Concentrations below the lower limit of quantification (5 µg/mL) are set to zero.

Source: End-of-Text Table 9.4.1

- **Population PK analysis**

A population PK model was developed using PK data from studies FIM, MONO, FAST, ILUSTRO Cohort 1A and 2, 8951-CL-0104, 8951-CL-0105, SPOTLIGHT, and GLOW (report 8951-PK-0005). It was based pooled dataset for PK modelling consisted of 714 patients from eight studies contributing with 5059 out of 5134 zolbetuximab concentrations. The final population PK model was a 2-compartmend model with zero order absorption and first order elimination and was updated during the reviewing process. Time-dependent CL was introduced an a slight change in covariates identified was observed during the updating step.

Special populations

The effects of various covariates on the pharmacokinetics of Zolbetuximab were assessed in population pharmacokinetic analyses.

- ***Impaired renal function***

The effect of renal function on the PK of zolbetuximab was evaluated using creatinine clearance (CrCL) calculated using the Cockcroft-Gault equation. Among the 714 patients, the majority of the study populations had normal renal function or mild renal impairment (42.9 % and 41.7 %, respectively). Only 15 % had a moderately impaired renal function and one patient (0.1 %) severe renal impairment. Renal function was not identified as a statistically significant covariate in the population PK model. No dose adjustments are proposed based on renal function.

- ***Impaired hepatic function***

The effect of hepatic function on the PK of zolbetuximab was investigated using the NCI-ODWG criteria. Mean AST was 26.1 U/L (range 7.8 – 202 U/L, median 20.1 U/L). Mean total bilirubin (TBI) was 0.455 mg/dL (range 0.006 – 3.501 mg/dL, median 0.375 mg/dL). Among the 714 patients, the vast majority of the study population had normal hepatic function (84.3 %). Only 15.1 % had a mildly impaired hepatic function, 0.6 % moderate impaired hepatic function and none had a severe hepatic impairment. Hepatic function was not identified as a statistically significant covariate in the population PK model. No dose adjustments are proposed based on hepatic function.

- ***Gender***

Among the 714 patients contributing to the population PK analysis, 37.7 % (n=269) were female and 62.3 % (n=445) male. During model development, sex was identified as a statistically significant effect on CLss of zolbetuximab. Compared to male participants, zolbetuximab CLss in female participants was 19.5% lower.

- ***Race/Ethnicity***

Among the pooled data for population PK analysis, 50.1 % (n=358) were Caucasian, 42.2 % (n=301) Asian, 0.8 % (n=6) Black, 2.7 % (n=19) others, and 4.2 % (n = 30) with missing information. Of the Asian population, 14.7 % (n=105) were Chinese, 10.2 % (n=73) were Japanese, and 9 % (n=64) were Korean. Race / Ethnicity was not identified as a statistically significant covariate in the population PK model. No dose adjustments are proposed based on Race / Ethnicity.

- ***Weight / Body surface area (BSA)***

Among the pooled data for population PK analysis BSA ranged from 1.13 to 2.5 m² (median=1.7 m², mean = 1.71 m²). BSA was identified as a statistically significant covariate on Clearances, and volume of distribution (V1 and V2). Clearances and volumes of distribution increased with increasing BSA. The proposed recommended doses are based on BSA.

- ***Elderly***

Among the pooled data for population PK analysis, mean age was 58.8 years (min = 22, max = 83 years, median = 61 years). In total, 32.2 % (n = 230) of the participants were > 65 years of age and 67.8 % (n = 484) ≤ 65 years. Overall, 5 % (n=36) were older than 75 years and 95 % (n= 678) < 75 years. During population PK model development, no statistically significant effect of age on the PK of zolbetuximab was identified. No dose adjustments are proposed based on age.

Table 10: Participants per age group in elderly

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	Total N= 207 (29.0%)	Total N=45 (6.3%)	Total N=0

- ***Children***

No PK data with zolbetuximab in paediatrics < 18 years of age are available. The safety and efficacy of zolbetuximab in children and adolescents below the age of 18 years have not yet been established. A waiver in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council has been granted.

- ***Tumour type***

Among the pooled data for population PK analysis, 540 participants (75.6 %) had gastric adenocarcinoma and 174 participants (24.4 %) had gastroesophageal junction adenocarcinoma. No statistically significant effect of tumour type on the PK of zolbetuximab was identified. No dose adjustments are proposed based for different tumour types.

- ***Sum of tumour diameter (SOD)***

Among the 714 patients included in the population PK analysis information on SOD was missing in 153. In all others, the mean SOD was 67.2 mm (min = 10 mm, max = 400 mm, median = 49.6 mm). No statistically significant effect of SOD on the PK of zolbetuximab was identified. No dose adjustments are proposed based on SOD.

- ***Claudin (CLDN) 18.2 expression***

Among the pooled data for population PK analysis, Claudin (CLDN) 18.2 expression was low (i.e. < 50%) in 1.4 % (n = 10), intermediate (i.e. 50% ≤ and < 75%) in 5 % (n = 36), and high (i.e. 75% ≤) in 90.8 % (n = 648) of the participants. Information on CLDN 18.2 expression was missing from n = 20 (2.8 %).

Due to a limited number of participants with low (N = 10, 1.4%) and intermediate (N = 36, 5.0%) expression level, CLDN18.2 was not evaluated as covariate during model development. No dose adjustments are proposed based CLDN 18.2 expression level.

- ***Serum albumin***

Patients included in the population PK analysis had serum albumin levels at baseline of 21 – 72.4 g/L (median = 39.1 g/L, mean = 38.9 g/L). CL decreased with increasing albumin. No dose adjustments are proposed based serum albumin levels.

- ***Prior gastrectomy***

Among the 714 patients included in the population PK analysis 225 (31.5 %) had gastrectomy and 489 (68.5 %) not. Based on the final updated population PK analysis, zolbetuximab Clearances were estimated to be lower and V1 to be slightly higher (10.3%) in participants with prior gastrectomy compared to those without prior gastrectomy. No dose adjustments are proposed based on gastrectomy status.

Pharmacokinetic interaction studies

A drug-drug interaction assessment of zolbetuximab and mFOLFOX6 components was performed in Cohort 2 of the ILUSTRO study. The blood samples to determine oxaliplatin (measured as total platinum

and free platinum) and 5-FU concentrations were collected after dosing mFOLFOX6 on cycle 1 day 1 (without zolbetuximab) and cycle 2 day 1 (with zolbetuximab).

Table 11: Summary of Chemotherapy Pharmacokinetic Studies

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route		Summary of Plasma Pharmacokinetic Parameters		
8951-CL-0103 (ILUSTRO) (Cohort 2)	Phase 2, open-label, multi-arm, non-randomized, multicenter Cohort 2: n = 21	Patients with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma whose tumors are CLDN18.2-positive§ Cohort 2: 12M/9F patients 58.86 (36, 74) years	Cohort 2 (Zolbetuximab 800/600 mg/m² + mFOLFOX6 Q3W)				
					C_{max_D}, (platinum/mL/mg) Mean (% CV) GeoMean, (% CV) GLSM n	AUC_{tlt_D}, h·µg/mL Mean (%CV) GeoMean, (%CV) GLSM n	t_{max}, hour Median (min, max) n
			Total platinum† Oxaliplatin dose: 85 mg/m²	C1D1	14.7 (16.1) 14.5 (16.3) 14.5 n = 21	194 (20.0) 190 (20.6) 190 n = 19	2.00 1.07, 2.45 n = 21
				C2D1	16.0 (21.7) 15.7 (23.3) 15.6 n = 19	218 (23.5) 212 (25.5) 210 n = 15	2.03 1.00, 2.10 n = 19
			Total platinum† Oxaliplatin dose: 85 mg/m²		GLSM ratio (90% CI)	GLSM ratio (90% CI)	NA
					107.41 (99.56, 115.88)	110.64 (103.08, 118.76)	NA
					C_{max_D}, platinum/mL/mg Mean (% CV) GeoMean, (% CV) GLSM n	AUC_{tlt_D}, h•platinum/mL/mg Mean (%CV) GeoMean, (%CV) GLSM n	t_{max}, hour Median (min, max) n
			Free platinum† Oxaliplatin dose: 85 mg/m²	C1D1	2.85 (34.2) 2.67 (41.0) 2.67 n = 20	28.7 (27.4) 27.7 (28.5) 27.7 n = 19	2.00 1.00, 2.33 n = 20
				C2D1	3.65 (30.6) 3.47 (35.1) 3.48 n = 18	33.4 (27.6) 32.5 (24.4) 32.2 n = 15	2.01 1.00, 2.08 n = 18
			Free platinum† Oxaliplatin dose: 85 mg/m²		GLSM ratio (90% CI)	GLSM ratio (90% CI)	NA
					130.43 (111.56, 152.49)	116.08 (103.53, 130.15)	NA

Study No.	Study Design	Patients No. (M/F) Age: mean (range)	Treatment Product, Dose, Route		Summary of Plasma Pharmacokinetic Parameters			
					C_{max_D}, ng/mL/mg Mean (% CV) GeoMean, (% CV) n	AUC_{tlt_D}, h•ng/mL/mg Mean (% CV) GeoMean, (% CV) n	AUC_{inf_D}, h•ng/mL/mg Mean (% CV) GeoMean, (% CV) n	t_{max}, hour Median (min, max) n
			5-FU‡ 400 mg/m² bolus +2400 mg/m² infusion	C1D1	1.34 (62.8) 1.11 (71.0) n = 20	0.972 (50.2) 0.867 (52.9) n = 20	2.52 (42.0) 2.32 (43.7) n = 19	0.500 (0, 45.8) n = 20
				C2D1	1.08 (58.4) 0.913 (74.6) n = 15	0.961 (42.5) 0.885 (44.3) n = 15	2.70 (27.0) 2.61 (28.1) n = 13	0.500 (0.333, 48.0) n = 16
			5-FU‡ 400 mg/m² bolus +2400 mg/m² infusion		GLSM ratio (90% CI)	GLSM ratio (90% CI)	GLSM ratio (90% CI)	NA
					83.00 (58.27, 118.25)	103.43 (80.82, 132.37)	117.19 (98.41, 139.55)	NA

Data cutoff: 03 May 2021 (ILUSTRO)

All participants who received at least 1 dose of study drug and for whom at least 1 pharmacokinetic measurement upon treatment was available (Pharmacokinetic Analysis Set).

5-FU: 5-fluorouracil; C: cycle; CI: confidence interval; CLDN18.2: claudin-18 splice variant 2; CV: coefficient of variation; D: day; F: female; GEJ: gastroesophageal junction; GeoMean: geometric mean; GLSM: geometric least squares mean; M: male; max: maximum; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; min: minimum; NA: not applicable; Q3W: every 3 weeks

† Total and free platinum parameters measured after administration of oxaliplatin, as part of mFOLFOX6 regimen alone (C1D1), or coadministered with zolbetuximab (C2D1)

‡ Parameters measured after administration of 5-FU, as part of mFOLFOX6 regimen, alone (C1D1), or coadministered with zolbetuximab (C2D1)

§ CLDN18.2 status is defined in [Table 1]

Source: [Study 8951-CL-0103 (ILUSTRO) Table 7, Table 8, Table 38 to Table 43].

Table 12: Impact of Covariates on Zolbetuximab Exposure Metrics (Revised Model)

GMR (90%CI)	BSA 5%	BSA 95%	ALB 5%	ALB 95%	HGB 5%	HGB 95%	TBILI 5%	TBILI 95%	Gastrectomy	Female
C_{max_1st}	0.994 (0.973, 1.015)	1.006 (0.985, 1.028)	0.999 (0.978, 1.021)	1.000 (0.979, 1.022)	0.905 (0.886, 0.925)	1.084 (1.061, 1.107)	1.026 (1.004, 1.048)	0.966 (0.946, 0.987)	0.912 (0.892, 0.931)	1.119 (1.096, 1.144)
AUC_{21d_1st}	1.008 (0.974, 1.043)	0.992 (0.959, 1.026)	0.930 (0.899, 0.962)	1.050 (1.015, 1.086)	0.989 (0.956, 1.023)	1.008 (0.974, 1.043)	1.003 (0.969, 1.037)	0.996 (0.963, 1.031)	1.339 (1.294, 1.385)	1.087 (1.051, 1.125)
C_{trough_1st}	1.027 (0.943, 1.119)	0.972 (0.892, 1.060)	0.793 (0.727, 0.864)	1.168 (1.072, 1.273)	1.055 (0.968, 1.150)	0.958 (0.879, 1.044)	0.986 (0.905, 1.075)	1.019 (0.935, 1.110)	2.140 (1.964, 2.332)	1.138 (1.045, 1.240)
C_{max_ss}	0.999 (0.982, 1.018)	1.001 (0.983, 1.019)	0.943 (0.926, 0.960)	1.042 (1.023, 1.061)	0.931 (0.915, 0.948)	1.061 (1.043, 1.081)	1.019 (1.001, 1.037)	0.975 (0.958, 0.993)	1.022 (1.004, 1.041)	1.159 (1.138, 1.180)
AUC_{21d_ss}	1.012 (0.984, 1.041)	0.988 (0.961, 1.016)	0.823 (0.801, 0.847)	1.124 (1.093, 1.156)	0.999 (0.971, 1.027)	1.001 (0.973, 1.029)	1.000 (0.973, 1.029)	1.000 (0.972, 1.028)	1.255 (1.221, 1.291)	1.214 (1.181, 1.249)
C_{trough_ss}	1.024 (0.975, 1.076)	0.976 (0.929, 1.025)	0.708 (0.674, 0.744)	1.216 (1.157, 1.277)	1.041 (0.991, 1.093)	0.968 (0.921, 1.017)	0.990 (0.942, 1.040)	1.014 (0.965, 1.065)	1.500 (1.428, 1.576)	1.323 (1.260, 1.390)
C_{ave}	1.011 (0.982, 1.041)	0.989 (0.960, 1.018)	0.830 (0.806, 0.855)	1.125 (1.093, 1.159)	0.997 (0.968, 1.026)	1.002 (0.974, 1.032)	1.001 (0.972, 1.030)	0.999 (0.970, 1.028)	1.298 (1.261, 1.336)	1.175 (1.142, 1.210)

ALB: albumin; AUC_{21d_1st}: area under the concentration-time curve from the time of dosing to 21 days after the first dosing; AUC_{21d_ss}: area under the concentration-time curve from the time of dosing to 21 days after the dosing at steady state; BSA: body surface area; C_{ave}: average concentration throughout the treatment; CI: confidence interval; C_{max_1st}: maximum concentration after the first dose; C_{max_ss}: maximum concentration at steady state; C_{trough_1st}: trough concentration after the first dose; C_{trough_ss}: trough concentration at steady state; GMR: geometric mean ratio; HGB: hemoglobin; TBILI: total bilirubin.

Pharmacokinetics using human biomaterials

Plasma protein binding of zolbetuximab was not performed as zolbetuximab is a monoclonal antibody. No other human biomaterials studies were conducted with zolbetuximab.

2.6.2.2. Pharmacodynamics

Mechanism of action

Zolbetuximab is a chimeric (mouse/human IgG1) monoclonal antibody directed against the tight junction molecule CLDN18.2. Nonclinical data suggest zolbetuximab binds selectively to cell lines transfected with CLDN18.2 or those that endogenously express CLDN18.2. Zolbetuximab depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Cytotoxic drugs were shown to increase CLDN18.2 expression on human cancer cells and to improve zolbetuximab-induced ADCC and CDC activities. In mice tumour models, zolbetuximab demonstrated an antitumour effect on CLDN18.2-expressing tumours injected subcutaneously and a combination of zolbetuximab with chemotherapy showed a more potent effect than zolbetuximab or chemotherapy alone.

Primary and Secondary pharmacology

Immunogenicity

To date, 9 clinical studies of zolbetuximab have been completed or are ongoing in adult patients with advanced adenocarcinoma of the stomach, oesophagus or GEJ whose tumours are CLDN18.2-positive. The immunogenicity profile of zolbetuximab has been characterized based on data from all of these 9 clinical studies and the results are summarized in the table below.

Table 13: Summary of Zolbetuximab Immunogenicity results from individual clinical studies

Study Identifier	Immunogenicity Assessment	Immunogenicity Results	Reference
Phase 1 Studies			
GM-IMAB-001 'FIM'	ADA samples were collected at D1 predose, and on D15 and D29	There was no evidence of ADA in the 15 participants (N = 3 per dose group) who received a single dose of zolbetuximab in the study. ADA incidence: 0/15 (0%)	[Study GM-IMAB-001 (FIM) CSR, Sections 12.1.2 and 12.1.3]
GM-IMAB-001-04 'PILOT'	ADA samples were collected predose of C1D1, at the EOT (21 days after last treatment) visit and every 9 weeks during the follow-up phase. In participants who continued zolbetuximab treatment after the Immunomodulation Phase (C1-C3), a predose sample was also collected at C5	Post-treatment samples from 27 out of 28 patients in the safety population were evaluated. Only one sample from one patient was detected as positive for ADAs after the end of treatment with a titer of 1:1. In all other samples, no post-treatment ADAs were detected. ADA incidence: 1/27 (3.7%)	[Study GM-IMAB-001-04 (PILOT) CSR, Section 11.5.2.5.3.3 Footnote 7]
8951-CL-0104	ADA samples were collected at predose on D1 of C1/2/3/5/9 and every 4 cycles ≥ C13, and at 30-day and 90-day follow-up visits	Among 18 participants (3, 3 and 12 participants in the Safety Part Arm A, Arm B and the Expansion Part, respectively) who had immunogenicity data after receiving at least 1 dose of zolbetuximab, 1 participant was positive for ADAs at baseline but was negative after receiving zolbetuximab. No participant with negative ADAs at baseline developed ADA positivity after receiving zolbetuximab. ADA incidence: 0/18 (0%)	[Study 8951-CL-0104 CSR, Section 6.4]
8951-CL-0105	ADA samples were collected at predose on D1 of C1/2/3/5/9/13/17, and at 30-day and 90-day follow-up visits	Among all the 12 participants who received zolbetuximab, 4 participants tested ADA only once at baseline (i.e., predose of C1D1) and 8 participants had more than 1 ADA test results after receiving at least 1 dose of zolbetuximab. No participant was confirmed positive for ADAs after receiving zolbetuximab treatment. ADA incidence: 0/8 (0%)	[Study 8951-CL-0105 CSR, Section 6.4]

Phase 2 or 2a Studies			
GM-IMAB-001-02 'MONO'	ADA measurements were conducted using pharmacokinetic samples (predose to 336 h after the EOI for the first dose; predose to 2 h after EOI for the fifth dose. Additional sparse samples were collected at predose for selected visits and after participants discontinued from treatment)	ADA data are available in 44 out of 54 participants who received zolbetuximab. One participant was tested for ADA only at baseline (i.e., predose of study day 1), and 43 participants had ADA test results at both baseline and after receiving at least 1 dose of zolbetuximab. No participant was confirmed positive for ADAs after receiving zolbetuximab treatment. ADA incidence: 0/43 (0%)	[Study GM-IMAB-001-02 (MONO) CSR, Section 8.5]
GM-IMAB-001-03 'FAST'	ADA samples were collected predose on C1D1, at the End of EOX Treatment, and every 12 weeks during the continued zolbetuximab treatment phase and the follow-up phase	Samples from 162 participants in arms 2 and 3 were analyzed. ADAs that developed de novo after administration of zolbetuximab were detected in samples from 2 patients. ADA incidence: 2/162 (1.2%)	[Study GM-IMAB-001-03 (FAST) CSR, Section 8.5]
8951-CL-0103 'ILUSTRO'†	ADA samples were collected at the following time points: Cohort 1A: Predose on D1 of C1/2/3/5/9/13/17 Cohort 2: Predose on C1D3, C1D22, C2D1, C2D22, D1 of C3/5/7/9 Cohort 3A: Predose on D1 of C1/2/3/5/9/13/17 All cohorts: 30-day and 90-day follow-up visits	Among 44 participants (21, 20 and 3 participants in cohorts 1A, 2 and 3A, respectively) who had immunogenicity data after receiving at least 1 dose of zolbetuximab, 3 participants with a negative baseline tested positive for ADA after receiving zolbetuximab. ADA incidence: 3/44 (6.8%)	[Study 8951-CL-0103 (ILUSTRO) CSR, Section 6.4]

Data cutoffs: 31 Jan 2019 (FAST); 03 May 2021 (ILUSTRO); 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW).
ADA: anti-drug antibody; BLA: Biological License Application; C: cycle; D: day; EOI: end-of-infusion; EOT: end of treatment; EOX: epirubicin, oxaliplatin and capecitabine.
†ILUSTRO has 4 cohorts. Cohort 4 (4A and 4B) is ongoing and not included in this BLA. Information about Cohorts 1A, 2 and 3 is provided.

Table 14: Immunogenicity Incidence of Zolbetuximab in First-line Patients with Gastric/GEJ Adenocarcinoma

	ILUSTRO Cohort 2 8951-CL-0103	SPOTLIGHT 8951-CL-0301	GLOW 8951-CL-0302	Total
Participants with at least 1 post-baseline sample (N)	20	256	229	505
Positive Participants (N)	1	8	21	30
Incidence (%)	5.0%	3.1%	9.2%	5.9%

GEJ: gastro-oesophageal junction;

Patients received zolbetuximab loading dose of 800 mg/m^2, followed by subsequent dose of 600 mg/m^2 every 3 weeks.

Data-cut-off: 03 May 2021 for ILUSTRO; 11 Nov 2023 for SPOTLIGHT/GLOW.

Assessment of Immunogenicity Impact on Pharmacokinetics, Efficacy and Safety

Pharmacokinetics

Participants with confirmed ADA positivity after receiving zolbetuximab were observed in Studies ILUSTRO Cohort 2 (n = 1), SPOTLIGHT (n = 8) and GLOW (n = 21). The overall immunogenicity incidence across these studies was 30/505 (5.9%).

Serum concentration-time profile were graphically compared to ADA negative patients. Due to the limited number of participants with positive ADA, a clear ADA impact on the PK of zolbetuximab could not be concluded. No dose adjustments are proposed based on ADA status.

Efficacy

Evidence of efficacy in the 29 participants from phase 3 studies (8 in SPOTLIGHT and 21 in GLOW) who were treatment-induced ADA positive were demonstrated. Out of the 29 participants, complete response was observed in 1 participant, partial response in 11 participants and stable disease in 4 participants.

Table 15: SPOTLIGHT and GLOW: Efficacy variables (PFS, OS, BOR and DOR) for treatment-induced ADA positive participants (Safety Analysis Set)

Study	PFS (mo)	OS (mo)†	BOR‡	DOR (mo)
SPOTLIGHT (Zolbetuximab plus mFOLFOX6)§	1.643+	29.372+	NE	-
	1.971+	9.659+	PR	0.033+
	4.205	4.205	SD	-
	6.472+	14.324+	PR	4.172+
	6.242	19.778	CR	4.370
	18.004+	18.004+	Non-CR/Non-PD	-
	4.140+	11.663	PR	1.774+
	15.803	15.803	SD	-
GLOW (Zolbetuximab plus CAPOX)§	5.618	5.618	PR	3.548
	7.786+	**8.148+**	**Non-CR/Non-PD**	**5.782**
	8.312	12.517+	PR	6.275
	4.107+	8.016+	Non-CR/Non-PD	-
	4.238	**9.363**	**PR**	**2.168**
	8.969+	15.869+	Non-CR/Non-PD	-
	8.148	**8.148**	**ND**	**-**
	10.415	**15.080+**	**Non-CR/Non-PD**	**-**
	6.407	**6.407**	**PR**	**4.238**
	0.033+	8.214	-	-
	12.616+	**14.522+**	**Non-CR/Non-PD**	**-**
	6.374+	**18.924+**	**Non-CR/Non-PD**	**-**
	3.877	3.877	PR	2.037
	5.815	5.815	SD	-
	1.051	1.051	-	-
	4.172+	11.992	PR	2.070+
	6.439	6.439	PR	2.267
	7.852+	14.390	Non-CR/Non-PD	-
	2.661	**2.661**	**-**	**-**
	1.873+	17.413	SD	-
	7.984	**7.984**	**PR**	**5.914**

Data cutoffs: Original submission: 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW); **new data cut**: 11 Nov 2023.

Bold text indicates participants that were included in the new data cut. Strikethrough text indicates participants that were not used for the generation of ADA-positive PK plots.

Treatment-induced ADA-positive included participants with 1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or 2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab.

ADA: anti-drug antibody; BOR: best overall response; CAPOX: capecitabine and oxaliplatin; CR: complete response; DOR: duration of response; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; NE: not evaluable; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease.

+ indicates censoring.

† OS is as per investigator assessment; rest of the variables are by independent review.

‡ Derived BOR based on all timepoint responses.

§ Individual subject identities are provided in the Appendices cited below.

Table 16: SPOTLIGHT and GLOW: Comparison of Progression-Free Survival by ADA Status (Full Analysis Set) of Participants Who Received Zolbetuximab

Parameter	SPOTLIGHT/GLOW	
	ADA Positive (N=29)	ADA Negative (N=509)
PFS Events, n (%)	15 (51.7)	268 (52.8)
Radiographical Progression	4 (13.8)	160 (31.5)
Death without Documented Progression	11 (37.9)	108 (21.3)
Censored, n (%)	14 (48.3)	240 (47.2)
Duration of PFS (Months) [1]		
Median (95% CI)	7.98 (5.82, 10.41)	9.30 (8.44, 10.58)
1st Quartile (95% CI)	5.62 (2.66, 6.44)	5.98 (4.50, 6.24)
3rd Quartile (95% CI)	15.80 (9.15, NE)	20.80 (17.81, 31.93)
Range [2]	0.03+, 18.00+	0.03+, 40.15+
Median Follow-Up Time, Months (95% CI) [3]	8.97 (6.37, 18.00)	13.50 (11.56, 15.21)
PFS Rate, % (95% CI) [4]		
At 6 months	69.78 (46.56, 84.43)	74.76 (70.40, 78.57)
At 12 months	25.83 (7.65, 49.03)	43.31 (38.16, 48.35)
At 18 months	12.92 (1.06, 39.83)	28.35 (23.17, 33.74)
At 24 months	NE (NE, NE)	21.23 (15.71, 27.33)
At 30 months	NE (NE, NE)	19.60 (13.81, 26.14)
At 36 months	NE (NE, NE)	16.33 (9.45, 24.86)
At 42 months	NE (NE, NE)	NE (NE, NE)

Participants were considered as ADA positive if (1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or (2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab. Otherwise, participants were considered as ADA negative. SPOTLIGHT: 8951-CL-0301 study, GLOW: 8951-CL-0302 study, ADA: anti-drug antibody; KM: Kaplan-Meier; NE: Non-Estimable; PFS: progression free survival. PFS: time from randomization until death from any cause or radiographic disease progression (per RECIST 1.1), whichever occurs first. Censoring rules are defined in each study SAP.
[1] Based on KM estimate.
[2] + indicates censoring.
[3] Based on reverse KM estimate.
[4] PFS rate and 95% CI are estimated using KM method and Greenwood formula.

Table 17: SPOTLIGHT and GLOW: Comparison of Overall Survival by ADA Status (Full Analysis Set) of Participants Who Received Zolbetuximab

Parameter	SPOTLIGHT/GLOW	
	ADA Positive (N=29)	ADA Negative (N=508)
Deaths, n (%)	18 (62.1)	275 (54.1)
Censored, n (%)	11 (37.9)	233 (45.9)
Censored at Cutoff Date, n (%)	1 (3.4)	34 (6.7)
Duration of Overall Survival (Months) [1]		
Median (95% CI)	11.99 (7.98, 19.78)	16.69 (15.51, 18.23)
1st Quartile (95% CI)	6.44 (3.88, 9.36)	8.54 (7.89, 9.30)
3rd Quartile (95% CI)	19.78 (14.39, NE)	28.91 (25.26, 33.68)
Range [2]	1.05, 29.37+	0.03+, 42.09+
Median Follow-Up Time, Months (95% CI) [3]	15.87 (12.52, 29.37)	19.81 (17.64, 21.49)
Overall Survival Rate, % (95% CI) [4]		
At 6 months	79.31 (59.64, 90.13)	84.71 (81.18, 87.63)
At 12 months	49.41 (29.71, 66.40)	63.77 (59.10, 68.05)
At 18 months	30.50 (12.01, 51.40)	45.52 (40.37, 50.52)
At 24 months	15.25 (1.38, 43.77)	34.71 (29.40, 40.07)
At 30 months	NE (NE, NE)	23.02 (17.54, 28.96)
At 36 months	NE (NE, NE)	16.47 (10.92, 23.01)
At 42 months	NE (NE, NE)	12.35 (5.56, 22.01)

Participants were considered as ADA positive if (1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or (2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab. Otherwise, participants were considered as ADA negative. SPOTLIGHT: 8951-CL-0301 study, GLOW: 8951-CL-0302 study, ADA: anti-drug antibody; KM: Kaplan-Meier; NE: Non-Estimable. Censoring rules are defined in each study SAP.
[1] Based on KM estimate.
[2] + indicates censoring.
[3] Based on reverse KM estimate.
[4] Survival rate and 95% CI are estimated using KM method and Greenwood formula.

Table 18: Summary of Objective Response Rate With Confirmation, Independent Review, by ADA Status (Full Analysis Set) of Participants Who Received Zolbetuximab

Parameter	SPOTLIGHT/GLOW	
	ADA Positive (N=29)	ADA Negative (N=508)
Best Overall Response (BOR), n (%) [1]	26 (89.7)	440 (86.6)
Complete Response (CR)	0	20 (3.9)
Partial Response (PR)	8 (27.6)	168 (33.1)
Stable Disease (SD)	8 (27.6)	128 (25.5)
Non-CR/Non-PD	8 (27.6)	85 (16.7)
Progressive Disease (PD)	0	26 (5.1)
Not Evaluable (NE)	1 (3.4)	5 (1.0)
No Disease (ND)	1 (3.4)	8 (1.6)
Not Available [2]	3	68
Objective Response Rate (ORR), n (%)	8 (27.6)	188 (37.0)

95% CI for ORR (%) [3]	(12.73, 47.24)	(32.80, 41.37)
Disease Control Rate (DCR), n (%) [4]	24 (82.8)	401 (78.9)
95% CI for DCR (%) [3]	(64.23, 94.15)	(75.13, 82.40)

Participants were considered as ADA positive if (1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or (2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab. Otherwise, participants were considered as ADA negative. SPOTLIGHT: 8951-CL-0301 study, GLOW: 8951-CL-0302 study. ADA: anti-drug antibody; CI: confidence interval.
[1] The definition for BOR followed RECIST 1.1. Confirmation of CR or PR occur at least 4 weeks following the initial assessment at which CR or PR is observed. When SD (or NON-CR/Non-PD) is believed to be best response, the assessment should be at least 8 weeks after randomization. For calculation of percentages, denominator includes the total number of subjects in each arm.
[2] No post baseline imaging assessment.
[3] Using exact method based on binomial distribution (Clopper-Pearson).
[4] Confirmed DCR was defined as the proportion of subjects who have a best overall response of CR, PR (≥4 weeks), SD or Non-CR/Non-PD (≥8 weeks).

Safety

Table 19: SPOTLIGHT/GLOW: Overall Summary of TEAEs (Safety Analysis Set) by Treatment-Induced ADA Positive/Negative Participants

	Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Positive N=29 n (%)	**Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Negative N=504 n (%)**
TEAE	29 (100.0)	500 (99.2)
Drug-related TEAE†	29 (100.0)	494 (98.0)
Serious TEAE	19 (65.5)	226 (44.8)
Drug-related Serious TEAE†	14 (48.3)	120 (23.8)
TEAE with CTCAE Grade ≥ 3	24 (82.8)	403 (80.0)
Drug-related TEAE with CTCAE Grade ≥ 3†	20 (69.0)	343 (68.1)
TEAE Leading to Death	5 (17.2)	44 (8.7)
Drug-related TEAE Leading to Death†	2 (6.9)	9 (1.8)

ADA: Anti-drug antibody; CAPOX: Capecitabine and oxaliplatin; CTCAE: common terminology for adverse events; mFOLFOX6: Modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; TEAE: treatment-emergent adverse event.
†Adverse events with a reasonable possibility of relationship as assessed by the investigator, or missing relationship were shown

Table 20: SPOTLIGHT/GLOW: Summary of Treatment-Emergent Adverse Events of Interest: Investigator Assessed Infusion Related Reactions Occurring in ≥ 3 Participants with Treatment-Induced ADA Positive/Negative (Safety Analysis Set)

Preferred Term (MedDRA v25.0)	**Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Positive N=29 n (%)**	**Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Negative N=504 n (%)**

Any Investigator-Assessed IRRs	17 (58.6)	198 (39.3)
Vomiting	11 (37.9)	103 (20.4)
Nausea	7 (24.1)	121 (24.0)
Chills	5 (17.2)	8 (1.6)
Flushing	3 (10.3)	5 (1.0)
Hypertension	3 (10.3)	10 (2.0)
IRR	3 (10.3)	14 (2.8)

Treatment Induced ADA positive includes subjects with (1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or (2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab.

All rest of subjects who do not belong in cases (1) or (2) (including subjects who were ADA negative, had only baseline ADA data or had only post-baseline data) will be summarized in Treatment Induced ADA negative.

ADA: Anti-drug antibody; CAPOX: Capecitabine and oxaliplatin; IRR: infusion related reaction; mFOLFOX6: Modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin.

Table 21: SPOTLIGHT/GLOW: Summary of Hypersensitivity Reactions Occurring in ≥ 2 Participants with Treatment-Induced Changes in ADA Status (Safety Analysis Set)

Preferred Term (MedDRA v25.0)	**Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Positive N=29 n (%)**	**Zolbetuximab plus mFOLFOX6 or CAPOX Treatment-induced ADA Negative N=504 n (%)**
Any Hypersensitivity Reactions	11 (37.9)	180 (35.7)
Stomatitis	2 (6.9)	64 (12.7)
Infusion related reaction	3 (10.3)	14 (2.8)
Erythema	2 (6.9)	8 (1.6)
Rash	2 (6.9)	21 (4.2)
Flushing	4 (13.8)	7 (1.4)

ADA: Anti-drug antibody; CAPOX: Capecitabine and oxaliplatin; mFOLFOX6: Modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin.
Treatment Induced ADA positive includes subjects with (1) negative ADA at baseline and positive ADA after receiving zolbetuximab; or (2) positive ADA at baseline and higher ADA titer after receiving zolbetuximab.
All rest of subjects who do not belong in cases (1) or (2) (including subjects who were ADA negative, had only baseline ADA data or had only post-baseline data) will be summarized in Treatment Induced ADA negative. Number of subjects (n) and percentage of subjects (%) are shown.

2.6.3. Discussion on clinical pharmacology

Zolbetuximab (formerly known as IMAB362; inventive name Vyloy) is a chimeric (mouse/human) IgG1 antibody directed against the tight junction molecule CLDN18.2. CLDN18.2 is a highly tissue-specific cell surface molecule that is expressed in normal gastric tissue as well as in many human cancers. Upon target binding, zolbetuximab mediates cell killing by antibody-dependent cellular cytotoxicity and complement dependent cytotoxicity.

No studies were conducted in healthy volunteers with zolbetuximab. This is considered acceptable as the first in human trial was in the oncology setting. The clinical pharmacology characterization is based on data from 9 clinical studies. The PK of Zolbetuximab was evaluated by NCA and population PK modelling.

The proposed posology is a i.v. single loading dose of 800 mg/m² Zolbetuximab and maintenance dose of 600 mg/m² of Zolbetuximab every 3 weeks or 400 mg/m² every 2 weeks. No comprehensible and adequate dose finding study was performed during the clinical development program. The proposed dosing regimen of 800 mg/m² Zolbetuximab and maintenance dose of 600 mg/m² of Zolbetuximab every 3 weeks has been tested in Phase 2 and Phase 3 studies with and without chemotherapy and clinical data has been provided.

Pharmacokinetics

- **Bioanalytical methods**

To determine serum concentration of Zolbetuximab in human serum and to determine ADAs against Zolbetuximab in human serum two different bioanalytical methods each, ELISA and ECLIA, has been applied and evaluated in four different test facilities and were used for different studies during the clinical development program.

PK-assay

In the **early clinical development program an ELISA assay** was validated to detect quantitatively Zolbetuximab concentration in human serum. This assay was used for the clinical study samples from **Study FIM and Study MONO**. However, based on the data provided, the validation method G08-030 is not in accordance with the EMA Guideline *(ICH guideline M10 on bioanalytical method validation)* and is not considered valid and reliable to measure/quantify serum concentrations of zolbetuximab in human serum (clinical study samples).

Even though the data from the early studies are quite small compared to the available data from the studies conducted in the later clinical development, since the PK samples are not available for re-analysis and the method used for their analysis has not been correctly validated, the samples from FIM and MONO studies have been excluded from the Population PK and simulation analysis data set.

In the **later clinical development program an ECLIA assay** was validated in three different test facilities to detect Zolbetuximab concentration in human serum. This assay was used in the clinical study samples from **Study FAST, Study ILUSTRO, Study 8951-CL-0104, Study 8951-CL-0105, Study SPOTLIGHT and Study GLOW**. The main characteristics of a bioanalytical method as precision and accuracy, selectivity, matrix effect, hemolysis, lipemia, sensitivity, stability (room temperature stability, sample processing temperature, long-term stability and Freeze-thaw stability) were evaluated adequately and the data met predefined acceptance criteria and are in accordance with the ICH guideline M10 on bioanalytical method validation (EMA/CHMP/ICH/172948/2019).

Although the study sample analysis and ISR data appeared to be acceptable and valid, in each study analysis, samples were measured outside the validated long-term stability time. However, methods 8951-ME-0005 and 8951-ME-0009 have ongoing stability testing contracted and the stability data will be updated as testing is completed for these methods. According to the applicant, stability testing has been extended for method 8951-ME-0009 up to 1100 days at -70°C or below for both zolbetuximab alone and in combination with mFOLFOX6 or CAPOX and thus only 10 samples out of 3645 samples tested are currently outside of stability. However, long-term stability data (Methods 8951-ME-0005 and 8951-ME-0009) should be provided in the final sample analysis reports, once stability testing is completed (REC).

ADA-assay

In the early clinical development program an ELISA assay and in the later clinical development program, multi-tiered ECLIA assays, were developed and validated to anti-IMAB362 antibodies in human serum. However, no full validation in accordance with the guidelines has been provided for the ELISA or ECLIA assays used for analyzing the clinical study samples from study GM-IMAB-001 [FIM], GM-IMAB-001-04 [PILOT], GM-IMAB-001-02 [MONO] and Study FAST. Although, the ADA tests are only semi-quantitative, based on the information provided the assays appeared not to be sufficient for a reliable analysis of clinical study samples. However, as these methods are no longer in use after transition to Astellas, no additional work can be performed. None of these studies were pivotal and the ADA data from these studies are not considered for the immunogenicity incidence of zolbetuximab in the SmPC.

In addition, also the ECLIA assay (validation report SLB500-829) developed and used for the analysis of clinical study samples collected from participants outside of China in the pivotal study **GLOW** and **SPOTLIGHT** was not fully validated in accordance with the guideline. The drug tolerance was considered too low at the concentrations for adequate detection of ADAs in the studies. Therefore, a new method has been developed and validated by the applicant to replace method 8951-ME-0008. The method validation report of the new method 8951-ME-0016 and the re-analysed data from study GLOW and SPOTLIGHT will be provided in Q3 2024 (REC).

The ECLIA assay (validation Report 8951-ME-0006 [180935VLC_ANI_R2]) developed and used for the analysis of clinical study samples collected from participants from China in the pivotal study GLOW and SPOTLIGHT was validated in accordance with the guideline. The results met the acceptance criteria for the analytical items and thus based on the available information the assay judged suitable for detection of anti-IMAB362 antibody in human serum by ECLIA.

Neutralizing antibody (NAb)-assay

No information/data was found in the submitted data package whether the samples identified as positive in the confirmatory assay were further characterized in neutralization assays. Although, only a low number of ADAs has been detected in the studies, it is important to characterize neutralizing activity of ADA with neutralization assays because the impact of ADA on safety and efficacy may correlate with NAb activity rather than ADA incidence. According to the applicant, multiple configurations and strategies were tested, and no assay with a reliable and accurate ability to detect low titer values could be established. Based on the available data from the limited ADA-positive patients Zolbetuximab appeared to have a low immunogenicity and the data did not suggest significant effects on zolbetuximab PK, efficacy, or safety. However, since there were concerns about the suitability of the ADA assay method 8951-ME-0008 (SBL500-829) to analyze pivotal clinical samples, a new method has been developed and validated by the applicant to replace method 8951-ME-0008. In case the re-analyses of ADA samples show a higher incidence of ADA positive samples and thus a higher immunogenicity of zolbetuximab compared to the current ones, further effort will be made to develop a validated NAb assay and NAb data will be provided (REC).

- ***ADME***

Zolbetuximab is administered as IV infusion and is therefore 100% bioavailable. The **mean Zolbetuximab concentration** increased rapidly, with the median time to maximum concentration (tmax) reached shortly after the end of infusion as expected for monoclonal antibodies. The Cmax for the proposed posology of Zolbetuximab 800/600 mg/m² Q3W were more or less comparable between studies.

During the procedure, an updated population PK analysis was submitted providing an estimated mean steady state volume of distribution of zolbetuximab of 5.5 L.

The **mean clearance** of Zolbetuximab appears consistent between the model-based analysis and NCA (0.015 L/h versus 0.012 – 0.029 L/h, respectively).

Zolbetuximab clearance (CL) decreased over time, with a maximal reduction from baseline values of 57.6% resulting in a population mean steady-state clearance (CL_{ss}) of 0.0117 L/h.

In addition, the estimated **half-life** of Zolbetuximab of 44 days by the original population pharmacokinetics analysis differs from the observed mean t1/2 range in the non-compartmental analysis (5.83 days- 21.7 days). Based on the updated population PK analysis, the half-life of zolbetuximab ranged from 7.6 to 15.2 days during treatment.

Zolbetuximab is expected to be catabolised into small peptides and amino acids.

Dose proportionality and time dependency

Dose proportionality after IV administration of zolbetuximab doses was analysed. The relationship between dose and exposure is considered dose proportional if the 95% confidence interval (CI) for the slope includes 1.0. Based on the provided data in the PK Report Amendment for **study GM-IMAB-001 (FIM)**, the descriptive statistics of the parameters Cmax, AUC28d and AUCinf and the statistical power analysis appear to be more or less dose proportional (slope includes 1.0). However, the data for the 600 mg/m² did not fully support the dose proportionality. After 168 hours the serum concentration was similar to the 300 mg/m² concentration. In addition, linearity appears also not unequivocally given based on the observed mean PK parameters (e.g. mean AUCinf, mean CL and mean Vz). Nevertheless, it needs to be considered that only 3 patients were included in each dosing group and moderate variability was observed. However, based on all the limited data available, the zolbetuximab exposure can be approximately considered dose-proportional. Nevertheless, zolbetuximab trough concentrations took longer time to reach steady state as estimated and differ between the clinical studies. For example, in **Study SPOTLIGHT and GLOW** it appears that the observed Ctrought steady state was actually not reached after end of study, i.e. C9D1 and C17D1, respectively. Upon request, the applicant provided the two following hypotheses for the longer time of zolbetuximab Ctrough to reach steady state in the phase 3 studies: 1) the actual t1/2 might be longer than initially estimated by NCA (which was based on limited sampling, spanning from the initiation of dosing to 21 to 28 days after dosing) and 2) zolbetuximab exhibits a time dependent PK with CL decreasing over time. In addition, no TMDD is expected according to the applicant and the reason for the time-dependent decrease in CL remains unclear.

Overall, based on the data available, it appears that zolbetuximab shows approx. dose proportionality, but the time dependency of zolbetuximab stays unclear. Thus, since no additional information is available, the PK profile of Zolbetuximab appears to be not well characterized during the clinical development and some uncertainties regarding the PK profile of Zolbetuximab remain. However, this does not appear to have a negative impact on the benefit/risk ratio.

Intra- and inter-individual variability

Based on the non-compartmental analysis low to moderate interindividual variability for Cmax and low to high interindividual variability for AUC and Ctrough as assessed by %CV was observed in the clinical studies.

Drug-Drug-Interaction

No formal DDI studies have been performed with zolbetuximab. This is acceptable considering that zolbetuximab, as monoclonal antibody, is not metabolized via cytochrome P450 (CYP) enzymes and thus is not expected to induce or inhibit CYP enzymes or to be a drug transporter. Therefore, the risk of drug-drug interaction is considered low for zolbetuximab. However, in Cohort 2 of the ILUSTRO study (n=21 participants), zolbetuximab was co-administered with Oxaliplatin or 5-FU and drug-drug-interaction assessment was performed. The effect on the pharmacokinetic parameters (AUC24h_D and Cmax_D) by co-administration of Zolbetuximab with Oxaliplatin or 5-FU was between 7% and 17%, except for Cmax_D of free platinum which was even higher (30%). Thus, the exposure of free oxaliplatin appears to be affected when co-administered with zolbetuximab. This could be relevant to the exposure-safety relationship since an increase in the free fraction of oxaliplatin could likely to be directly linked to an increase in safety concerns. In contrast, the observed effect on the exposure of 5-FU and total oxaliplatin when co-administered with zolbetuximab is currently not considered to be clinically relevant. Nevertheless, the number of samples tested was small (n=13-20) and the results should be interpreted with caution. In addition, mFOLFOX6 did currently not appear to affect the pharmacokinetics of

Zolbetuximab in a clinically significant manner. Therefore, the tested dosing regimen does not suggest any relevant changes in exposure of zolbetuximab after co-administration of mFOLFOX.

Immunogenicity

Based on a pooled analysis of data from two phase 3 studies, the overall immunogenicity incidence was 4.4% (21 of 479 total patients treated with zolbetuximab 800/600 mg/m² every 3 weeks in combination with mFOLFOX6/CAPOX were tested positive for anti-drug antibodies [ADAs]). Because of the low occurrence of ADAs, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown.

However, since method 8951-ME-0008 (SBL500-829) appeared not fully reliable and thus there were concerns regarding assay suitability to analyse clinical samples, a new method (8951-ME-0016) has been developed and validated to replace method 8951-ME-0008 and to re-analyse at least the samples from the pivotal studies SPOTLIGHT and GLOW. Once reliable ADA results from a suitable full validated method with a sufficient drug tolerance limit are available, pooled ADA data (from the same indication across all studies, analysed with the same or comparable validated assay method that perform equally) will be submitted and presented in the SmPC (REC).

Effect of ADA status on PK

To evaluate the effect of ADA positivity on PK an overlay plot of zolbetuximab serum concentration-time profile of participants with ADA positive and negative by study was presented. Based on these data most datapoints by participants with positive ADAs detected were within the range of datapoints by participants with negative ADAs across studies. Although, some datapoints of ADA positive patients showed low to no zolbetuximab concentration, this was also observed for some ADA negative patients and thus no clear evidence was observed that treatment-induced positive ADAs affect PK in general.

However, based on the box plots provided for exposure for ADA positive versus ADA negative participants by study (SPOTLIGHT and GLOW) along with a summary of primary and secondary PK statistics based on NCA, a trend was observed that positive ADAs have an impact on the PK of Zolbetuximab in later treatment cycles (approx. from cycle 5 and onwards). In addition, all ADA positive participants with an ADA titer >2000 have no or just a low Zolbetuximab concentration based on the plot provided. Therefore, it might be that high ADA titers (>2000) could have an effect on PK. However, it needs to be considered that the number of treatment-induced ADA positive patients was in general low across the studies (n=29) and the number of patients with high ADA titers (>2000) were even lower. Thus, more data would be required for a meaningful conclusion whether ADAs in general or only high ADA titers (>2000) have an impact on PK or not. In addition, no neutralizing antibodies has been analysed. Neutralizing antibodies (NAbs) refer to those ADAs with the ability to interfere with interactions between the therapeutic protein product and its target. It is important to characterize neutralizing activity of ADA because the impact of ADA on pharmacokinetics, pharmacodynamics, safety, and efficacy may correlate with NAb activity rather than ADA incidence. However, based on the limited ADA positive participants no final conclusion can be drawn, whether the positive ADAs have a relevant impact on the PK of Zolbetuximab.

Effect of ADA status on Efficacy

The potential effect of ADA status on efficacy was evaluated based on the PFS, OS, BOR and DOR results of the ADA positive patients from study GLOW (n=21 ADA positive patients) and SPOTLIGHT (n=8 ADA positive patients). A direct comparison between ADA positive and ADA negative participants has been provided.

The **PFS event** in both, ADA positive and ADA negative participants were comparable. Radiographical progression was lower in ADA positive participants compared to ADA negative participants. However, numerically more death without documented progression was observed in ADA positive participants

(11/29 [37.9%]) compared to ADA negative participants (108/509 [21.3%]). In addition, the median duration of PFS, the median follow-up time and the PFS rates were numerically lower in ADA positive participants compared to ADA negative participants.

Similar results were observed for **Overall Survival**. Numerically more deaths were observed in ADA positive participants (18/29 [62.1%]) compared to ADA negative participants (275/508 [54.1%]). In addition, the median duration of OS, the median follow-up time and the OS rates were numerically lower in ADA positive participants compared to ADA negative participants.

Overall, although the number of ADA positive patients is low, the number of ADA positive participants are currently questionable overall, based on concerns regarding assay suitability of method 8951-ME-0008 (SBL500-829) to analyse pivotal clinical samples. However, a trend that positive ADAs could have an effect on efficacy was observed and cannot be excluded so far based on limited data. Moreover, no analysis of neutralizing antibodies has been performed. Nevertheless, based on the limited ADA positive participants no final conclusion can be drawn. It is further acknowledged that the results might be impacted by different prognostic baseline characteristics between the ADA-positive and ADA-negative subgroups, as immunogenicity status can only be determined post randomization.

Effect of ADA status on safety

Based on the provided data the total number of TEAEs and drug-related TEAEs was similar between treatment-induced ADA positive patients (n=29 [100%] each) and ADA negative patients (n=500 [99.2%]; n=494 [98%]). However, more serious TEAEs and drug-related serious TEAEs have been reported in treatment-induced ADA positive patients (n=19 [65.5%]; n=14 [48.3%]) compared to ADA negative patients (n=226 [44.8%]; n=120 [23.8%]). In addition, TEAE leading to death and drug-related TEAE leading to death was numerically higher in treatment-induced ADA positive patients (n=5 [17.2%]; n=2 [6.9%]) compared to ADA negative patients (n=44 [8.7%]; n=9 [1.8%]). Based on this limited data a trend appears that treatment-induced ADAs might have an effect on safety with regard to serious TEAEs.

In contrast, TEAE with CTCAE Grade ≥3 and drug-related TEAE with CTCAE Grade≥3 were similar between treatment-induced ADA positive patients (n=24 [82.8%]; n=20 [69.0%]) and ADA negative patients (n=403 [80.0%]; n=343 [68.1%]).

The incidence of any investigator-assessed IRRs was higher in treatment-induced ADA positive patients (n=17 [58.6%]) compared to ADA negative patients (n=198 [39.3]). Based on the preferred term the incidence of vomiting, chills, flushing, hypertension and IRR was higher in treatment-induced ADA positive patients (n=11 [37.9%]; n=5 [17.2%]; n=3 [10.3%]; n=3 [10.3%] and n=3 [10.3%]) compared to ADA negative patients (n=103 [20.4%]; n=8 [1.6%]; n=5 [1.0%]; n=10 [2.0%] and n=14 [2.8%]). Only nausea was comparable between ADA positive and ADA negative patients (n=7 [24.1%] and n=121 [24.0%]).

The incidence of any hypersensitivity reaction was similar between treatment-induced ADA positive patients (n=11 [37.9%]) compared to ADA negative patients (n=180 [35.7%]). Based on the preferred term the incidence of infusion related reaction, erythema, rash and flushing was higher in treatment-induced ADA positive patients (n=3 [10.3%]; n=2 [6.9%]; n=2 [6.9%] and n=4 [13.8%]) compared to ADA negative patients (n=14 [2.8%]; n=8 [1.6%]; n=21 [4.2%]; and n=7 [1.4%]). Only stomatitis was a bit lower in treatment-induced ADA positive patients (n=2 [6.9%]) compared to ADA negative patients (n=64 [12.7%]).

Overall, although the number of ADA positive patients is low, a trend that positive ADAs could have an effect on safety was observed and cannot be excluded so far based on limited data. Moreover, no analysis of neutralizing antibodies has been performed. However, based on the limited ADA positive participants no final conclusion can be drawn.

In **conclusion**, due to the low incidence of positive ADAs, data are too limited to draw a final clinically meaningful conclusion. However, since a potential trend that treatment-induced ADAs might have an impact on pharmacokinetics, efficacy or safety in participants treated with zolbetuximab cannot be excluded at present, the text currently provided in the SmPC "[..] Because of the low occurrence of ADAs, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown." is considered adequate and is supported. Nevertheless, the number of ADA positive participants were questionable overall, based on concerns regarding assay suitability of method 8951-ME-0008 (SBL500-829) to analyse pivotal clinical samples. Therefore, a new method has been developed and validated by the applicant to replace method 8951-ME-0008. The data are expected to be available by Q3 2024. In case the updated datasets show different results compared to the current ones, updated analysis on the impact of ADA status on Pharmacokinetics, Efficacy and Safety should be provided (REC).

Pharmacometrics (pop PK and exposure-response analyses)

A population PK model was originally developed using data from overall eight clinical studies including data from patients with locally advance unresectable or metastatic gastric or GEJ adenocarcinoma, three Phase 1 studies (Studies GM-IMAB-001, 8951-CL-0104, 8951-CL-0105), three Phase 2 studies (Studies MONO, FAST and ILUSTRO) and two Phase 3 studies (Studies SPOTLIGHT and GLOW). Purpose of the model was to characterise the PK of zolbetuximab, investigate the influence of covariates and alternative dosing regimen. Exposure metrics were generated that were also used in subsequent exposure-response analyses.

The proposed dosing regimen (loading dose 800 mg/ m^2 followed by 600 mg/ m^2 Q3W) was tested in studies FAST, 8951-CL-0104, 8951-CL-0105, ILUSTRO, SPOTLIGHT, and GLOW, contributing with PK data from 714 patients. Study PILOT also investigated this dosing regimen, but no PK data were collected there. The proposed alternative dosing regimen (loading dose 800 mg/ m^2 followed by 400 mg/ m^2 Q2W) was selected based on population PK model simulations only.

The Applicant has performed an analysis to compare different dosage regimens. The Q3WBSA (800/600 mg/m^2 Q3W) used in phase 3 studies with the alternative Q2WBSA (800/400 mg/m^2 Q2W) dosage regimen were compared with GMRs of exposure metrics of all the participants.

The use of a model-based approach in order to investigate the new proposed dosage regimen is endorsed. However, as there are no clinical data to confirm the appropriateness of the new posology, the use of the model is considered of high impact. Those models need to be shown to perform sufficiently reliable and credible, especially when replacing clinical studies. This appears the situation here for the alternative proposed dosing regimen. However, it was doubted that the PK of zolbetuximab is well described by the presented model. The credibility of the originally proposed final population PK model was questioned and its usage in subsequent analyses was considered not supported. It was concluded that no dose selection should be done based on this model. Thus, a revision of the model was considered required (part of former pharmacokinetic MO and OCs). Moreover, it seemed that results from NCA and those from population PK modelling analysis were not consistent (see below), which supported the hypotheses that the model is not sufficiently reliable, or maybe the presentation of the results were not entirely correct.

Another important aspect that was needed to be considered in the follow-up discussions was that the quality and thus acceptability of the bioanalytical methods used to analyse the PK in studies FIM and MONO were questioned (please refer to the respective section). Consequently, for it was considered uncertain, whether PK data from these studies can be used to robustly contribute to the determination of the PK behaviour of zolbetuximab (part of former pharmacokinetic MO).

Additionally, the Applicant did not provide any information and rationale regarding the pre-defined targeted serum exposure (metrics) and therapeutic window of zolbetuximab. However, this is a very crucial point that needs to be clarified also to conclude on the alternative dosing regimen.

A comprehensive update in pop PK modelling was requested. The Applicant implemented the time-dependency in PK (featured a time-independent CL and a time-dependent decaying CL) when updating the former pop PK model. This is referred to as the current final model in the following. Overall, a similar model performance is observed between the refined and the original population PK model, despite some discrepancies have been identified on the median tendency of some cohorts depicted in the pc-VPC's that highlight the inadequacy of the popPK model structure to fully capture the observed PK behaviour.

Methods and Data

Original model development was initiated based on a previously developed population PK model (8951-pk-0001; not included in the submitted package) with data from studies ILUSTRO, 8951-CL-0104 and 8951-CL0105. The same 2-compartment model with zero-order input and first order elimination was used as an initial structural model for the current analysis.

The base model includes inter-individual variability in the PK parameters CL, Vc and Vp and a mixed error model. BSA effect was included on CL, Q, Vc and Vp. Subsequently, additional covariates were tested in the PK parameters. The final population PK model includes four additional covariate effects. GAST, ALB and SEX on CL and GAST on Vp. Moderate inter-individual variability has been characterized in the final model in the PK parameters CL (39.6%) and VC (25.8%) and high interindividual variability in Vp (97.6%). The Applicant was asked to further discuss the potential reasons for this high variability of this monoclonal antibody. Overall, the lack of sufficient PK evidence together with the large half-life of zolbetuximab impeded to properly characterize the distribution process between the central and peripheral compartment, which could explain the large IIV on Vp since no IIV on Q was incorporated. The population PK model has been updated to better characterize the time-dependency on CL, which partially reduced the IIV on parameters related to the peripheral compartment (Q), but still large IIV on disposition parameters were estimated due to the experimental deficiencies collecting PK evidence.

The random effects were assumed to be symmetrically and independently distributed with a zero mean, suggesting adequate characterization of the random effects. Covariates were grouped when less frequent (<10 %). A stepwise forward inclusion and backward elimination procedure for covariate selection was selected. This is acceptable, but due to the current findings it is not clear if there was a problem with the performed covariate analysis. The effect of ADAs was therefore only assessed graphically only.

The random effects for V1 appeared to have a relevant trend in the Comb1 (EOX), suggesting a non-random distribution of the individual V1 across the combination therapy. Comb1 has not been evaluated as a covariate in the SCM building procedure. Thus, the Applicant was requested to evaluate Comb1 as a covariate during the SCM building procedure. The MAH recognized that a trend between ETA-V1 and Comb1 (EOX) was observed, although the clinical relevance is low since EOX was not included in the target indication. As suggested, the MAH updated the population PK model incorporating EOX on V1, which led to a statistically significant reduction of the OFV, with a reduction on the IIV of V1 (23.6% to 20.1%). The proposed modification of the population PK model is endorsed.

In the provided report 8951-PK-0005, it is shown that 56 samples were excluded because of error in bioanalytical assay procedure, elapsed time is negative, and sampling time is unknown or missing. According to that table, seven samples were outliers. Thus, there appears to be a discrepancy between the numbers of excluded samples in the table (56 samples) compared to the description in the report

(68 samples). This issue was clarified. The number of BLQ at the non-safety follow-up visit was 68, which was not linked to the samples excluded.

The analysis contained 714 subjects (540 with stomach cancer and 174 with GEJ adenocarcinoma) and a total of 5134 observations. Data below the limit of quantification were set to 0 and then excluded. However, LLOQ was 1 µg/mL for studies FIM, MONO, FAST, and 5 µg/mL for all other studies. Therefore, the Applicant was asked to clarify which LLOQ was assumed for the pooled dataset and to explain again how these data were handled. In response, the Applicant indirectly replied to the requested topics. In the pooled dataset, all BLQ values were set to 0. The number of BLQ records was considered limited and thus, it was assumed that the M3 method does not impact population PK modelling.

Renal function was calculated using Cockcroft-Gault. Hepatic impairment was categorised by National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, based on AST and total bilirubin. Information on the equation that was used to calculate BSA was not provided or could not be found and was thus requested to be provided. The Applicant detailed that the formulas used for calculating BSA for each study contributing to the population PK analysis were different and not consistently chosen. In the analysis data set, Mosteller was used for FIM, MONO, ILUSTRO, CL-0104 and CL-0105 and DuBois was used for FAST. BSA data for SPOTLIGHT and GLOW was taken from case report form data, in which the pharmacy manual allows the site to calculate BSA according to the site's preferred formula and they were not consistent. A comparison of BSA value used in analysis, for Mosteller formula and DuBois formula was provided by the Applicant, indicating that BSA values across data were overall comparable, as also indicated by pop PK modelling. Nevertheless, inconsistencies in the formula used for calculating BSA imply one source of variability, that also affects results from SPOTLIGHT and GLOW, where the method for calculation was not reported.

It was further concluded that demographic information should include also body weight and body size of the patients included in the analysis. Information on demographics was updated to include summary statistics of weight and height of patients included in the population PK analysis, which is appreciated. Nevertheless, it is still unclear how baseline BSA was calculated. This represents one source of uncertainty, nevertheless, it is considered, that this is not the main source that issues PK description, and the description of demographics seems plausible. This, the issue is considered not further pursued.

For model evaluation and qualification common methods were used, which is acceptable. However, pcVPC were only presented on linear scale and should be presented on semi-log scale, as well. Moreover, additional VPCs and GOF plots were requested. Plots were provided accordingly using the updated pop PK model. Overall, the updated population PK model seems to properly describe the disposition of zolbetuximab with no relevant bias on short timescale; however, at longer timescale, in particular the median predicted observations are observed to no match the observed Phase III data (consistent bias: underprediction) which is still of concern.

Further, model-predicted vs observed exposure plots indicate that Cmax_1st is constantly underpredicted. However, in the response provided to the MO this was not consistent with this finding but more with the results where, Cmax_1st mean (385 µg/mL) and median (371µg/mL) were predicted to be lower than those observed and even lower than those values detailed in the 454 and 442 µg/mL, meaning an overprediction of observed Cmax_1st compared to observed (419 µg/mL (mean) and 391 (µg/mL) median). Similar trends are observed for AUC21d (mean: 2176 day*µg/mL median: 2104 day*µg/mL vs 2015 day*µg/mL and 1963 day*µg/mL compared to observed: 2130 day*µg/mL (mean) and 2011 day*µg/mL (median). In case these values could be regarded credible, there would indeed some accumulation in Cmax be indicated. However, this assumption contradicts the presented results. The Applicant was thus asked to discuss and clarify these inconsistencies between simulated

exposure and model diagnostics, taking the potential accumulation of Cmax that is expected from a dose-proportional drug assuming linear PK into account. It was clarified that the simulations were based on different assumptions, namely consideration of EOX treatment, that is not included in the target indication. As this was incorporated as a covariate (on V1) in the updated revised final pop PK model, the explanation provided can be followed. The overall trend in underestimating Cmax_1st for the studies provided (FAST, ILUSTRO, 8951-CL-0104, 8951-CL-0105) is however remaining.

The predictability for overall use of context for pop PK modelling (description of PK and prediction/justification for alternative Q2W posology) is still of concern. In this line, it is noted that the revised model exhibited notable shrinkage in peripheral compartment-related parameters (Q, V2). This is because the majority of analysis population was from phase 3 studies, where PK sampling was sparsely conducted, resulting in insufficient information about second phase for those patients (compared to those in phase 1 or phase 2 studies with more intensive PK sampling). Because removing IIV on these parameters resulted in a statistically significant worsening of the OFV, the inclusion of IIV on both was chosen as the final model. IIV in CL, V1, and V2 were low to high. Although zolbetuximab is doses are based on BSA, IIV in V2 is still pronounced. Nevertheless, overall, a similar model performance is observed between the refined and the original population PK model, despite some discrepancies have been identified on the median tendency of some cohorts depicted in the pc-VPC's that highlight the inadequacy of the popPK model structure to fully capture the observed PK behaviour.

Modelling results:

The table of descriptive statistics of primary and secondary PK parameters required an update (P5, P95, and %CV should be included). For comparison results of primary and secondary PK parameters using NCA and population PK modelling were required. Summary statistics for Cmax_1st and AUC21d after the first dose of 800 mg/m2, and CL estimated by NCA and population PK model were provided. A table was requested to list descriptive statistics of primary and secondary PK parameters (including P5, P95, and %CV). Besides Cmax_1st, AUC21d_1st (800 mg/m2) and CL (L/day), no other PK parameter such as volume of distribution or t1/2 were detailed, which hinders the direct comparison. In addition, CL are split in the pop PK model and were estimated to 0.0117 L/h (0.281 L/day) and 0.0159 L/h (0.382 L/day), respectively, for time-independent CL and a time-dependent decaying CL for zolbetuximab. CL was calculated to CL = CLss + CLT * exp(-Kdecay * time). The Vss was 5.53 L and t1/2 ranged 7.56 to 15.2 days, but no comparison with NCA was provided with this response. Of note, model-predicted vs observed exposure plots indicate that Cmax_1st is constantly underpredicted. Although t1/2 derived from the current model is now closer to the NCA derived value, it is overall regarded short for a monoclonal antibody. As CL is assumed to be time-dependent, also an increase in t1/2 is expected until an apparent steady state would be reached.

The clearance appears consistent between model-based analysis and NCA (0.015 L/h versus 0.012 – 0.025 L/h in Study FIM, respectively), but the claimed $t_{1/2}$ of 43.6 days appeared too high and is neither consistent with the NCA results (13.1 – 21.7 days, study FIM), nor consistent with results calculated using the parameter estimates of the final model. The volume of distribution appeared inconsistent between model-based analysis and NCA (16.4 L versus 6.56 – 8.9 L in Study FIM, respectively). Moreover, the volume of distribution for the peripheral compartment appears comparably high for such a compound. This was requested to be reviewed and justified. The observed difference in estimated zolbetuximab PK profiles between the population PK model and NCA were acknowledged by the Applicant. Two reasons have been provided that may account for these differences, the limited sampling time after drug administrations and the slower achievement of Ctrough_ss observed in phase 3 studies. Two potential hypotheses were considered: first, the actual t1/2 might be longer than initially estimated by NCA, aligning with the originally submitted linear 2 compartment population PK model (43 days (pop PK) vs less than 11 days (NCA)); second, zolbetuximab exhibits a time-dependent PK with CL decreasing over time. While the first hypothesis is

considered plausible in terms of PK of a full monoclononal antibody not showing TMDD or non-linear kinetics (resulting in an apparent terminal t1/2 of about 21 days), the pharmacological reasons why zolbetuximab clearance is indicated to be time-dependent with CL decreasing over time is currently not known.

Structural and covariate model parameters were estimated with relatively good precision (RSE <20%).

GOF plots showed, in general, adequate model performance also of the updated model in the DV vs PRED and DV vs IPRED, however some discrepancies could be detected between observed and population predicted data, especially underprediction of high values based on data from 8951-CL-0104. Moreover, it was not clear whether the chosen data can be pooled or not for these analyses. As model diagnostics and predictive checks indicate difficulties in describing data from early studies, in particular the median trends in FIM and late phase PK data from Phase III studies at longer time scale and issues from bioanalytics that could not be solved, exclusion of PK data that are deemed uncertain may help in achieving a more adequate description of Phase III data (SPOTLIGHT; GLOW) and that would support the derivation of credible PK characteristics. This is considered important for reflecting those in SmPC (medium impact) and to derive exposure predictions for the Q2W regimen to justify the alternative dosing (high impact). Maybe the inclusion of unbalanced data in terms of peripheral distribution or very sparse data (Phase III) could also have influenced the pc-VPC. In this regard, it would be unjustified to fully rely only on pc-VPC to decide whether the popPK model could serve to justify a more conservative posology which provides the same dose amount corrected by the interval for a drug with linear PK properties. GOF, parameter estimates and low residual error were obtained, suggesting that the overall description of the longitudinal PK data was acceptably achieved (but with obvious bias in the relevant Phase III studies). Nonetheless, the Applicant was requested to investigate by sensitivity analysis the impact on pop PK model performance when excluding FIM and MONO PK data from the PK analysis data set (also resulting from studies affected by assay limitations). Both pop PK model parameter estimates and covariates, based on the differential PK data set, appeared overall similar, including notable shrinkage. In consequence, however, the pc-VPCs as assessed previously still are found to underpredict the median (Ctrough of Phase III study GLOW and SPOTLIGHT in steady state).

Another very important point of discussion is the question why zolbetuximab is proposed to be dosed based on BSA (mg/m²) and not by body weight (mg/kg). It is understood that other treatments (e.g. cytotoxic compounds) for this patient population are dosed based on BSA. Nonetheless, as of today, most antibodies are either dosed per kg body weight or using flat (fixed) doses and there exist only a few that are dosed by BSA. The proposed BSA based dosing of zolbetuximab is seen critically and is not preferred from a practical point of view, due to a risk of potential medication errors. The Applicant was thus asked to re-investigate the population PK model for zolbetuximab (i) using BSA and (ii) including body weight instead of BSA as part of the covariate analysis as an alternative approach. Based on the simulation results provided, it is agreed that there was no obvious difference between BSA-based final model and WT-based final model. Thus, the selection of the BSA-based model used for other analyses for responses is supported. Due to concern about possible medication errors based on uncommon mg/m² dosing, the Applicant was asked to discuss whether it could be justified to recommend an alternative weight-based dose recommendation. If a weight-based dose regimen cannot be sufficiently justified, a respective statement for highlighting was requested to be stated in the SmPC. As all clinical data were achieved with this dosing scaled by m2, it is acceptable that the Applicant does not consider weight-based dosing for recommendation. The argumentation that chemotherapy dose is calculated in mg/m2, aligning zolbetuximab dosing units with the same measure offering a convenient and practical approach for physicians can be understood. The Applicant agrees to further highlight in the SmPC that individual patient doses should be calculated based on BSA rather than body weight, which is acknowledged.

The proposed dosing regimen includes a loading dose of 800 mg/m² for the very first zolbetuximab administration. However, no justification was provided for this. Given that, the proposed dosing scheme is Q3W application, steady state appears roughly achieved after the second dose (i.e. first dose of 600 mg/m²) and that some safety events appear associated with C_{max} after 800 mg/m², this loading dose is currently not understood and supported. A justification for the 800 mg/m² loading dose was required. The Applicant argued that based on the simulation using the revised population PK model (modified clearance), the loading dose of 800 mg/m2 is expected to achieve higher median Ctrough and Cave during the initial cycles (approximately 33% and 5% to 17% higher after the first and second infusions, respectively) when compared to 600 mg/m2 as the initial dose and consequently, the percentage of patients to achieve the targeted Ctrough of 50 µg/mL is doubled in the group receiving a higher loading dose. Simulation results further indicate that the loading dose of 800 mg/m2 is expected to be beneficial to patients, especially during their initial treatment cycles, however these findings are highly dependent on the choice of the model and implementation of CL. Overall, if regarded compelling, the level of 50 µg/mL is reached fast for the majority of subjects, regardless of a loading dose. On the other hands, patients had a higher incidence of nausea and vomiting during the first zolbetuximab infusion with lower frequency in subsequent doses/cycles. The Applicant argues that this observation is not specific to zolbetuximab but was also observed for the placebo arm and for Study MONO, in which zolbetuximab was dosed as 600 mg/m2 Q2W without a loading dose. The Applicant's arguments can overall be followed and given statistically significant and clinically meaningful improvements in PFS and OS shown in clinical studies incorporating the loading dose of 800 mg/m2, the inclusion of 800 mg/m2 as a loading dose can be agreed.

The revised population PK model predicted that Q2WBSA will have about 21% lower Cmax at steady state and 19% to 40% higher Ctrough across treatment periods when compared to the Q3WBSA regimen.

Special populations

Zolbetuximab is mainly cleared from the body by degradation. Therefore, its clearance is not expected to be affected by renal or hepatic function in a relevant fashion.

Population PK analyses did not show any impact of mild (N=298) or moderate (N= 109) renal impairment on the exposure of Zolbetuximab. The effect of severe renal impairment on the PK of zolbetuximab is unknown.

No dose adjustment is required in patients with mild (creatinine clearance [CrCL] ⩾60 to <90 mL/min) or moderate (CrCL ⩾30 to <60 mL/min) renal impairment. No dose recommendation has been established in patients with severe renal impairment (CrCL ⩾15 to <30 mL/min).

Population PK analyses did not show any impact of mild (N=108) hepatic impairment on the exposure of Zolbetuximab. The effect of moderate hepatic impaired patients (N=4) is limited to fully understand whether differences in exposure do exist. No PK information of zolbetuximab was collected in patients with severe hepatic impairment.

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin [TB] ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN, or TB >1 to 1.5 × ULN and any AST). No dose recommendation has been established in patients with moderate (TB >1.5 to 3 × ULN and any AST) or severe (TB >3 to 10 × ULN and any AST) hepatic impairment.

Based on the population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified based on gender [62.3% male, 37.7% female] or race [50.1% Caucasian, 42.2% Asian, 4.2% Missing, 2.7% Others, and 0.8% Black].

Population pharmacokinetic analysis indicates that age [range: 22 to 83 years; 32.2% (230/714) were >65 years, 5.0% (36/714) were >75 years] did not have a clinically meaningful effect on the pharmacokinetics of zolbetuximab.

No dose adjustment is required in patients ≥65 years of age. Data for patients aged 75 years and older who received zolbetuximab are limited.

The PK properties in children have not been characterized. There is no relevant use of zolbetuximab in the paediatric population in the treatment of gastric or gastro-oesophageal junction adenocarcinoma.

Exposure-response analyses

The exposure-response analyses are basically performed for data from one zolbetuximab dosing regimen (800 mg/m² loading dose followed by 600 mg/m² maintenance dose Q3W) and a few data after administration of 1000 mg/m² Q3W. Therefore, answering the question whether the currently proposed dose is preferable over any other is not substantially informed by results from these analyses. No dedicated dose finding studies that would support a more comprehensive (dose)-exposure-response relationship analysis were conducted.

Further, there is no defined therapeutic window. A serum exposure of zolbetuximab Ctrough of 50 µg/mL or higher is targeted. This threshold has been selected based on the half maximal effective concentration of in vitro ADCC and CDC activities. It is not related to any clinical endpoint. This hampers the interpretability of exposure-response analyses, although the switch to the modified regimen would imply a more balanced exposure at steady state in terms of higher Ctrough_ss and lower Cmax_ss expected compared to the 600 mg/m² Q3W regimen.

Several exposure metrics were evaluated for efficacy (Cave_last, Ctrough_1st, Ctrough_last, AUCtau_last, T>31_21d_1st, T>50_21d_1st, T>100_21d_1st) and safety endpoints (Cave_event, Cmax_1st, Cmax_last, AUCtau_last, Cave_9w, InfT1st, InfR1st), which is endorsed. The exposure metrics were estimated using actual dosing records.

E-R analysis with regard to efficacy

Investigation of an exposure-efficacy relationship was conducted using PFS/PFSL, OS, DOR/DORL, ORR/ORRL and DCR/DCRL as efficacy parameters in patients from the phase 2 study (FAST) and the two phase 3 studies (SPOTLIGHT and GLOW). PFS / PFSL, OS and DOR / DORL were explored by Kaplan-Meier estimates and exposure metrics based on the former pop PK model.

Participants with higher exposures tended to have a longer PFS and PFSL. Q1 and Q2 seems to have shorter PFS and PFSL than CHEMO treatment. In the multivariable Cox proportional hazard modelling analysis for PFS and PFSL all exposure metrics were identified as statistically significant predictors, demonstrating that a clear exposure-efficacy relationship exists.

Kaplan-Meier curves of OS showed that higher exposure (Q3 and Q4) seems to have longer OS. Q1 and Q2 seems to have shorter OS than CHEMO treatment. In the multivariable Cox proportional hazard modelling all exposure metrics were again identified as statistically significant predictors.

There appears to be a slight trend of a relationship between C_{ave_last}, C_{trough_last} and AUC_{tau_last} and ORRL, but none with ORR. Chemotherapy (EOX, CAPOX) and non-measurable lesion appear to be associated with a lower probability of ORRL. Given that non-measurable lesion was found to be associated with a longer survival and longer DORL, this seems somewhat contradictive and this should be interpreted with caution. Non-measurable disease at baseline appears associated with a progression free survival and longer survival. However, this should be interpreted with caution.

From what is understood, there appears not to be a clear trend for improvement in the probability of DCR(L) with zolbetuximab compared to placebo and no difference between zolbetuximab exposure (quartiles).

Kaplan-Meier curves of OS showed that higher exposure (Q3 and Q4) seems to have longer OS. Q1 and Q2 seems to have shorter OS than CHEMO treatment. In the multivariable Cox proportional hazard modelling all exposure metrics were again identified as statistically significant predictors.

Subsequently, the relationship between Cave_last quartiles and the demographic covariates identified as statistically significant for PFS and OS were further explored. The results showed that there are more participants in the Q1 and Q2 exposure percentiles that have worse ECOG status, measurable disease and have larger SOD. ECOG, non-measurable disease, EOX and CAPOX were related to greater changes in the hazard ratio compared to Cave_last, indicating that the clinical relevance of changes in exposure in the range of the proposed dosing regimens is very limited.

Kaplan-Meier curves and multivariate logistic regression analyses of DOR / DORL, ORR/ORRL, DCR/DCRL showed that higher exposure (Q3 and Q4) seems to have longer efficacy DOR / DORL, ORR/ORRL and DCR/DCRL. In all of them, except DCR/DCRL, additional covariates were included in addition to Cave_last, whose Odds Ratio suggests a greater impact on efficacy than the changes in Cave_last observed with the proposed dosing regimens. Despite this, it would be highly informative to assess the clinical relevance of changes in exposure across different Cave_last percentiles among the different efficacy markers that show a significant relationship with exposure. Regarding Exposure-response, the Applicant was thus requested to provide exposure-efficacy / survival analyses by exposure subgroups for the lower (Q1, Q2) compared to the higher (Q3, Q4) exposure quartiles. In response, the requested analysis has been provided, however stratified by exposure quartiles in terms of Cave. It is not fully understood which data or timepoint influenced Cave. As no therapeutic window has been established, and Q2W and Q3W regimen are expected to achieve different Ctrough levels, the Applicant was requested to rerun the analysis by also considering exposure quartiles of the relevant PK measure Ctrough. Results should be discussed accordingly, and the confidence intervals should be detailed describing the estimate effect. E-R analyses regarding safety should be considered. The requested analysis based on exposure (quartiles) in terms of Ctrough and Ctrough_ss, as shown to be highly correlated with Cave, were provided. A plausible relation with respect to efficacy based on Ctrough was shown in terms of lower Hazard Ratio of PFS and OS with Q2W dosing, that is expected to result in slightly higher Ctrough_ss in comparison with Q3W dosing, and in terms of exposure response in Ctrough_ss by quartiles (Kaplan_Meier-Plots provided). In contrast to E-R analyses based on Cave quartiles, results indicated that Ctrough_ss quartiles Q1 and Q2 are not expected to have a benefit greater than chemotherapy regarding both, OS and PFS.

E-R analysis with regards to safety

Investigation of an exposure-safety relationship was conducted using occurrence of TEAE of grade ≥ 3, combined gastrointestinal toxicity (nausea, vomiting and abdominal pain) of grade ≥ 3 or ≥ 2, combined toxicity (nausea and vomiting) of grade ≥ 3 or grade ≥ 2, anaemia of grade ≥ 3, neutropenia of grade ≥ 3, hypersensitivity reaction, infusion related reaction and potential infusion related reaction, and number of TEAEs of grade ≥ 3 within first 9 weeks as safety parameters in patients from the two phase 3 studies (SPOTLIGHT and GLOW) and the phase 2 study (FAST).

Several safety endpoints were evaluated across different exposure metrics through logistic regression models. A positive relationship has been identified between exposure and gastrointestinal AEs (GITX and GITX2), nausea and vomiting (GITXVN, GITXVN2), neutropenia (NT), infusion related reaction (IRR), and potential infusion related reaction (PIRR). For grade 3 adverse events, the predicted probability with exposure levels at the upper end of the Cmax_1st distribution is less than 40% and 20% for Cmax_1st values at the 50th percentile. For the rest of the safety markers, probabilities

greater than 50% and 70% at the upper end of the Cmax_1st. Therefore, factors associated with changes in exposure can obviously affect the safety profile of zolbetuximab. Similarly, Cmax_1st and AUCtau_last were found to be associated with safety endpoints. It was found that Asian as well as chemotherapy backbone (EOX, CAPOX) appear to be associated with a lower in probability of neutropenia. On the other hand, it was explained that observed neutropenia is likely caused by chemotherapy backbone rather than zolbetuximab. This is somewhat contradictory and should be interpreted with caution. The overall exposure, in terms of AUC or Cave, is expected to achieve very similar levels across both regimens. This would justify the change of regimen from the point of view of the efficacy endpoints, since no relevant changes in PFS and OS are expected. Due to differences in Cmax and Ctrough across both regimens it is uncertain whether the prediction performance of the multivariate logistic regression analyses on safety outcomes has improved, which may limit the conclusion about the absence of change in safety endpoints with the Q2W vs the Q3W regimen. As there is no evidence that can corroborate the predictions, the results of the safety analyses must be considered with caution.

By using the revised population PK model, the E-R analyses on efficacy (PFS and OS) and safety (gastrointestinal toxicity and IRR) were repeated. The results from the E-R analyses were consistent between the original model and the revised model.

Tumour dynamics analysis

A longitudinal PK/PD model considering the impact of zolbetuximab exposure on tumour dynamics was conducted, which is appreciated. The baseline tumour sum of diameters (SOD) were characterized with a linear growth process and saturable and linear killing of zolbetuximab and chemotherapy, respectively. A resistant rate constant parameter was included on SOD to account for the increase of SOD after treatment initiation with zolbetuximab. A very empirical model was proposed, thus quantitative model-based conclusions should be considered with caution. The mathematical framework's ability to characterize data from different cohorts is considered supportive. Model predicted relative change of SOD from baseline was provided to evaluate BSA or fixed-based Q3W vs Q2W regimens, indicating very similar longitudinal profiles over the 5th, 50th and 95th percentiles of exposure. Provided that the assumptions in this tumour dynamic modelling exercise are true, it might be suggested, that irrespective of the (simulated) dosing regimen, the effect on SOD is expected to be the same. Moreover, the results suggest a large variably in effect on SOD change from baseline, which is consistent with the large variability in zolbetuximab PK. To fully assess the final PKPD model performance, Pc-VPC in addition to the shown goodness-of-fit plots needed to be provided. The results suggest that the tumour growth inhibition model over-predicts the IIV, since 95% PI and simulated 5th and 95th percentiles provided lower and higher predictions than the corresponding 5th and 95th percentiles of the experimental data. This could impact model-based predictions of TGI with alternative dosing regimens in prospective analyses. Therefore, the current TGI model is considered for descriptive purposes and regulatory recommendations should not be established based on the current TGI model.

Relationship between zolbetuximab concentration and QTc

No thorough QT/QTc study has been performed to assess the impact on change in QT interval. Linear mixed-effects exposure-response modelling was conducted to characterize the relationship of change from baseline of QTcF (ΔQTcF) with Zolbetuximab serum concentrations. The impact on dQTcF prolongation for patients with hight Cmax levels (95th percentile) has been provided during the procedure based on the updated population PK model. The corresponding 95th percentile of Cmax (633 µg/mL) would lead to a mean dQTcF prolongation of 9.527 msec with <12.23 msec if considering the 85% CI. Based on these results, no clinically relevant QTcF prolongation is expected in patients receiving zolbetuximab, even for those patients with very high exposure (Cmax) levels.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology characterization is based on data from 9 clinical studies. The PK of Zolbetuximab was evaluated by NCA and population PK modelling. Based on the data available, the PK profile of Zolbetuximab appears to be not well characterized during the clinical development. Consequently, as no additional data are available, some uncertainties regarding the PK profile of Zolbetuximab remain. However, this does not appear to have a negative impact on the benefit/risk ratio.
Regarding the clinical pharmacology data following the alternative Q2W regimen, any PK and E-R information following 800/400 mg/m² Q2W relies on modelling and simulation analyses only.

The former pop PK model has been updated to better characterize the observed data (by mainly incorporating time-dependencies on CL). Although it can be concluded that NCA and pop PK results are considered more aligned, there are still deficiencies of the final population PK model identified that do also apply for the derived exposure predictions for the Q2W regimen. No relevant differences are expected in the overall exposure between Q3W and Q2W that would cause clinically relevant changes in the efficacy/safety balance.

Regarding E-R, using the revised population PK model, the E-R analyses on efficacy (PFS and OS) and safety (gastrointestinal toxicity and IRR) were repeated. It is concluded that the results from the E-R analyses were consistent between the original model and the revised model.

Thus, in conclusion, based on the totality of evidence and given that the clinically untested regimen is expected to achieve exposure ranges fully covered by the Q3W regimen and observed during the clinical development, the alternative Q2W regimen, being more convenient for patients receiving combination therapy following the same dosing interval, is deemed supported.

To complete the overall package on clinical pharmacology, the following RECs are being raised: The incidence of positive ADAs detected was low within and across the studies. Nevertheless, based on the limited data available, a trend that treatment-induced ADAs might have an impact on pharmacokinetics, efficacy or safety in participants treated with zolbetuximab cannot be excluded and is reflected in the SmPC. However, since there were concerns regarding method 8951-ME-0008, a new method, 8951-ME-0016, has been developed and validated to replace method 8951-ME-0008. The method validation report and re-analysed data from study GLOW and SPOTLIGHT are expected to be available by Q3 2024 (**REC).** In case the updated datasets show different results compared to the current ones, an updated analysis of the impact on ADA status on PK, efficacy and safety will be provided **(REC).** Moreover, in case the updated datasets show a higher immunogenicity of zolbetuximab compared to the current ones, the applicant is recommended to make further effort to develop a validated NAb assay and to provide NAb data **(REC)**.

2.6.5. Clinical efficacy

2.6.5.1. Dose-response studies

Dose-efficacy response relationship was explored during the early clinical development of zolbetuximab. The first-in-human study GM-IMAB-001 evaluated single doses of zolbetuximab monotherapy (33, 100, 300, 600, and 1000 mg/m² with 3 gastric cancer patients each). The MONO study applied repeated monotherapy doses of 300 mg/m² and 600 mg/m² Q2W; the evaluation of the lower dose of 300 mg/m² was limited to four patients (all patients had progressive disease). The 600 mg/m² Q2W monotherapy dose showed preliminary signs of efficacy in 40 enrolled patients with advanced G/GEJ adenocarcinoma; best overall response was PR in 4 participants (9.3%) and stable

disease in 6 participants (14.0%). No objective responses were reported for treatment with zolbetuximab monotherapy (applied dose about 600 mg/m² Q3W) in other early studies, including Cohort 1A of the ILUSTRO study (n=30), the PILOT study (n=19), and the two Phase 1 studies 8951-CL-0104 (n=18) and 8951-CL-0105 (n=12) in Japanese and Chinese subjects with advanced G/GEJ adenocarcinoma.

The FAST study evaluated zolbetuximab in combination with chemotherapy. A statistically significant PFS and OS benefit was observed when zolbetuximab 800/600 mg/m² Q3W was added to EOX chemotherapy vs EOX alone. A third arm with a 1000 mg/m² Q3W regimen of zolbetuximab plus EOX was added by protocol amendment. As claimed by the Applicant, the PFS and OS benefit of the 1000 mg/m² Q3W regimen was not superior to the 800/600 mg/m² Q3W regimen and was less tolerated with respect to gastrointestinal toxicity. Thus, the 800/600 mg/m² Q3W zolbetuximab regimen was selected as the recommended phase 3 dose for the SPOTLIGHT and GLOW studies.

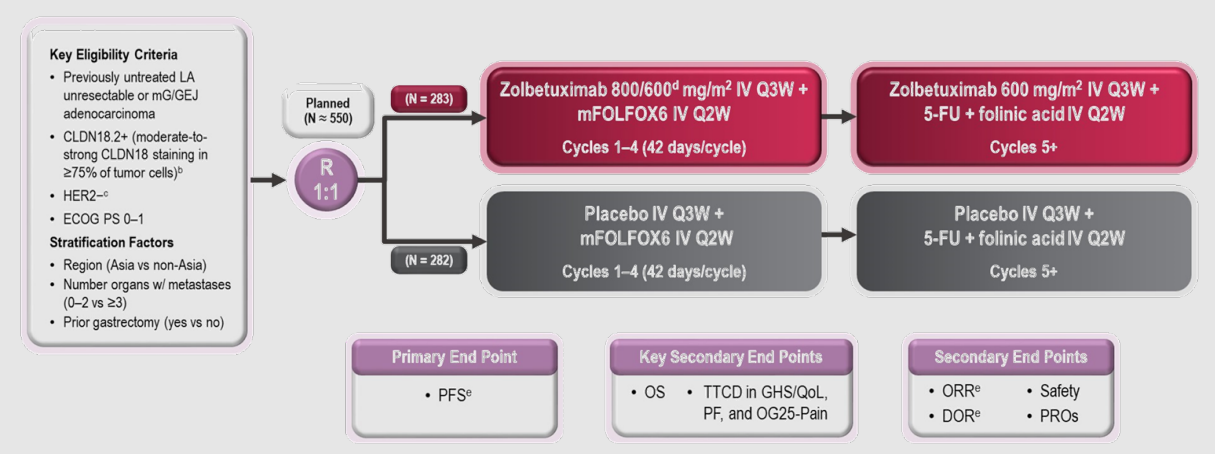
An every 2 weeks dosing regimen for zolbetuximab has been explored using a modelling approach. As concluded by the Applicant, a dose of 800/400 mg/m2 Q2W will reach similar efficacy and safety as the dose of 800/600 mg/m² Q3W (please refer to clinical pharmacology).

2.6.5.2. Main study SPOTLIGHT

Title: A Phase 3, Global, Multicenter, Double-blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (8951-CL-0301).

Methods

Figure 1: Spotlight Study Design



Radiologic imaging was evaluated every 9 weeks for the first 54 weeks and then every 12 weeks thereafter until the participant developed radiological disease progression per RECIST v1.1 or started other systemic anticancer treatment, whichever came earlier.

Study Participants

Key inclusion criteria:

- Participants were considered adults (e.g., ≥ 18 years of age in the United States) according to local regulation at the time of signing the informed consent.

- Participants must have had:
  - A histologically confirmed diagnosis of gastric or GEJ adenocarcinoma.
  - Radiologically confirmed locally advanced unresectable or metastatic disease.
  - Radiologically evaluable disease (measurable and/or non-measurable disease according to RECIST 1.1) per local assessment.
- Participant's tumour expressed CLDN 18.2 in ≥ 75% of tumour cells demonstrating moderate to strong membranous staining as determined by central IHC testing.
- Participant had a known HER2-negative tumour as determined by local or central testing on a gastric or GEJ tumour specimen.
- ECOG performance status 0 to 1.
- Predicted life expectancy ≥ 12 weeks in the opinion of the investigator.
- Participant must meet laboratory test results:
  - Haemoglobin ≥ 9 g/dL. Subjects requiring transfusions are eligible if posttransfusion haemoglobin ≥ 9 g/dL.
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Albumin ≥ 2.5 g/dL
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) without liver metastases (or < 3.0 x ULN if liver metastases are present)
  - AST and ALT ≤ 2.5 x ULN without liver metastases (or ≤ 5 x ULN with liver metastases)
  - Estimated creatinine clearance ≥ 30 mL/min
  - Prothrombin time/international normalized ratio (INR) and PTT ≤ 1.5 x ULN (except for subjects receiving anticoagulation therapy)

<u>Key exclusion criteria:</u>

- Prior systemic chemotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. However, participants may have received either neo-adjuvant or adjuvant chemotherapy, immunotherapy or other systemic anticancer therapies as long as it was completed at least 6 months prior to randomization. Participant may have received treatment with herbal medications that have known antitumor activity > 28 days prior to randomization.
- Radiotherapy for locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma ≤ 14 days prior to randomization and had not recovered from any related toxicity.
- Subject has received other investigational agents or devices within 28 days prior to randomization.
- Systemic immunosuppressive therapy, including systemic corticosteroids within 14 days prior to randomization (single dose of systemic corticosteroids allowed).
- Prior severe allergic reaction or intolerance to known ingredients of zolbetuximab or other monoclonal antibodies, including humanized or chimeric antibodies.
- Prior severe allergic reaction or intolerance to any component of study treatment.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Complete gastric outlet syndrome or a partial gastric outlet syndrome with persistent/recurrent vomiting.

- Per investigator judgment, subject has significant gastric bleeding and/or untreated gastric ulcers that would exclude the subject from participation per investigator judgment.
- Subject has a known history of a positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B (positive HBs Ag) or C infection.
- An active autoimmune disease that required systemic treatment within 3 months prior to randomization.
- An active infection requiring systemic therapy that has not completely resolved within 7 days prior to randomization.
- Significant cardiovascular disease including any of the following:
  - Congestive heart failure (defined as NYHA Class III or IV), myocardial infarction, unstable angina, coronary angioplasty, stenting, coronary artery bypass graft, cerebrovascular accident or hypertensive crisis within 6 months prior to randomization.
  - History of clinically significant ventricular arrhythmias (i.e., sustained ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes).
  - QTc interval > 450 msec for male participants; QTc interval > 470 msec for female participants.
  - History or family history of congenital long QT syndrome.
  - Cardiac arrhythmias requiring anti-arrhythmic medications (participants with rate-controlled atrial fibrillation for >1 month prior to randomization were eligible).

Subject has history of central nervous system metastases and/or carcinomatous meningitis from gastric/GEJ cancer.

Treatments

Arm A received zolbetuximab plus mFOLFOX6; Arm B received placebo plus mFOLFOX6.

Zolbetuximab was administered intravenously as an 800 mg/m2 loading dose followed by subsequent doses of 600 mg/m2 every 3 weeks (infusion for minimum of 2 hours). 0.9% Sodium Chloride was used for infusion solution preparation for both zolbetuximab arm and placebo arm.

mFOLFOX6 was administered intravenously over 2 hours or longer as oxaliplatin 85 mg/m² concurrent with folinic acid 400 mg/m² (or levofolinate 200 mg/m²), followed by a 5-FU 400 mg/m² intravenous bolus, followed by a continuous infusion of 5-FU 2400 mg/m² over 46 to 48 hours. All components of mFOLFOX6 were administered every 2 weeks for 4 or more cycles (3 treatments per cycle). Participants received up to 12 mFOLFOX6 treatments (or components of mFOLFOX6 if some components were discontinued due to toxicity). After 12 mFOLFOX6 treatments, participants could continue to receive 5-FU and folinic acid at the investigator's discretion until the participant met study treatment discontinuation criteria.

Antiemetic premedication was recommended to include NK-1 receptor blockers and 5-HT3 receptor blockers* (*with caution to subjects who have or may develop QTc prolongation). Since the impact of corticosteroids on the potential efficacy of zolbetuximab was not known, use of corticosteroids should be avoided or minimized unless required for management of an emergent medical condition (e.g., severe nausea/vomiting or hypersensitivity reaction).

Dose modification recommendation for zolbetuximab

Dose increase or dose reduction for zolbetuximab/placebo was not allowed.

Table 22: Dose modifications for Vyloy (from SmPC Table 2)

Adverse reaction	Severity[a]	Dose modification
Hypersensitivity reactions	Anaphylactic reaction, suspected anaphylaxis, Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. For the next infusion, premedicate with antihistamines and administer per the infusion rates in Table 3.
Infusion related reaction	Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. For the next infusion, premedicate with antihistamines and administer per the infusion rates in Table 3.
Nausea	Grade 2 or 3	Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. For the next infusion, administer per the infusion rates in Table 3.
Vomiting	Grade 4	Permanently discontinue.
	Grade 2 or 3	Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate[b] for the remaining infusion. For the next infusion, administer per the infusion rates in Table 3.

a. Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.
b. Reduced infusion rate should be determined per physician's clinical judgment based on patient tolerability, severity of toxicity, and previously tolerated infusion rate (see section 4.4 for patient monitoring recommendations).

To help minimise potential adverse reactions, it is recommended that each infusion is started at a slower rate than the initially calculated rate for the entire infusion, and gradually increased as tolerated during the course of the infusion.

Table 23: Infusion rates recommended for each Vyloy infusion (from SmPC Table 3)

Zolbetuximab dose		Infusion rate	
		First 30-60 minutes	Remaining infusion time[b]
Single loading dose (Cycle 1, Day 1)[a]	800 mg/m^2	75 mg/m^2/hr	150-300 mg/m^2/hr
Maintenance doses	600 mg/m^2 every 3 weeks Or 400 mg/m^2 every 2 weeks	75 mg/m^2/hr or 50 mg/m^2/hr	150-300 mg/m^2/hr or 100-200 mg/m^2/hr

a. The cycle duration of zolbetuximab is determined based on the respective chemotherapy backbone (see section 5.1).
b. In the absence of adverse reactions after 30-60 minutes, the infusion rate can be increased as tolerated.

Objectives/Endpoints

Table 24: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of zolbetuximab plus mFOLFOX6 compared with placebo plus mFOLFOX6 (as first-line treatment) as measured by PFS in participants with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma	PFS, defined as the time from the date of randomization until the date of radiological PD (per RECIST 1.1 by IRC) or death from any cause, whichever is earliest
Secondary	
• To evaluate efficacy as measured by OS (key secondary objective)	OS, defined as the time from the date of randomization until the date of death from any cause
• To evaluate the PF, OG25-Pain and GHS/QoL scores as measured by EORTC (key secondary objective)	TTCD (defined as time to confirmed deterioration, i.e., time from randomization to first clinically meaningful deterioration that is confirmed at the next scheduled visit) using the PF, OG25-Pain and GHS/QoL scores as measured by EORTC QLQ-C30 and QLQ-OG25
• To evaluate efficacy as measured by ORR	ORR, defined as the proportion of participants who have a best overall response of CR or PR as assessed by IRC per RECIST 1.1
• To evaluate efficacy as measured by DOR	DOR, defined as the time from the date of the first response (CR/PR) until the date of PD as assessed by IRC per RECIST 1.1 or date of death from any cause, whichever is earliest
• To evaluate safety and tolerability of zolbetuximab	Safety and tolerability, as measured by AEs, laboratory test results, vital signs, ECGs and ECOG performance status
• To further evaluate other HRQoL using additional parameters as measured by EORTC QLQ-C30, QLQ-OG25, Global Pain and EQ-5D-5L questionnaires	HRQoL using the additional parameters as measured by EORTC QLQ-C30, QLQ-OG25, Global Pain and EQ-5D-5L questionnaires
• To evaluate the pharmacokinetics of zolbetuximab	Pharmacokinetics of zolbetuximab, C_{trough}
• To evaluate the immunogenicity profile of zolbetuximab	Immunogenicity of zolbetuximab as measured by the frequency of ADA positive participants

Exploratory objectives/endpoints:

- **TTP**, defined as the time from the date of randomization until the date of progressive disease as assessed by the IRC per RECIST 1.1

- **PFS2**, defined as the time from the date of randomization until the date of radiological progressive disease (per investigator) following subsequent (second-line) anticancer therapy (ACT) or death from any cause, whichever was earliest
- **DCR**, defined as the proportion of participants who had a best overall response of stable disease, CR or PR as assessed by IRC per RECIST 1.1
- Potential genomic and/or other exploratory **biomarkers** that may correlate with treatment outcome of zolbetuximab and mFOLFOX6; *Note*: will be presented in a separate report
- **Health resource utilization** (HRU)

Sample size

550 participants were planned to be recruited in order to collect 300 PFS events and 396 OS events. The planned 300 PFS events during the study provide 93.4% power to detect a difference in PFS between zolbetuximab plus mFOLFOX6 with the assumption of 9 months median PFS time and placebo plus mFOLFOX6 with the assumption of 6 months median PFS time (HR = 0.67) at the 1-sided 0.025 significance level. Similarly, the planned 396 OS events during the study provide 81% power to detect a difference in OS between zolbetuximab plus mFOLFOX6 with the assumption of 14.7 months median survival time and placebo plus mFOLFOX6 with the assumption of 11 months median survival time (HR = 0.75) at the 1-sided 0.025 significance level.

Randomisation and blinding (masking)

The study was planned as double-blind and randomised on a 1:1 ratio. Randomization of subjects was planned to use blocked randomization and be stratified by Region (Asia vs. Non-Asia), Number of Organs with Metastatic Sites (0 to 2 vs. ≥ 3), and Prior Gastrectomy (Yes vs. No).

Statistical methods

All efficacy analyses were planned to be run on the Full Analysis Set (no Per Protocol Set defined as by final protocol). Hypotheses testing on the primary and key secondary endpoints PFS and OS between Arm A (zolbetuximab) and Arm B (placebo) was planned to be performed using log-rank test stratified by Region (Asia vs. Non-Asia), Number of Organs with Metastatic Sites (0 to 2 vs. ≥ 3) and Prior Gastrectomy (Yes vs. No). In addition, stratified Cox proportional hazards model was planned to be used to estimate the hazard ratio and the corresponding 95% confidence interval.

Table 25: PFS Primary Analysis Definition (based on IRC radiological assessments only) (source: Table 1, SAP)

Situation	Date of Event or Censoring	Outcome
No baseline imaging assessments	Date of randomization	Censored
No evaluable post-baseline imaging assessments, no death	Date of randomization	Censored
Subject did not receive new anti-cancer therapy (ACT):		
Radiological PD documented per RECIST v1.1	Date of first radiological PD (defined as earliest of date of scan showing new lesion if PD is based on new lesion or date of last scan of target lesions if PD is based on increase in sum of diameters (SOD) of target lesions)	Event
No radiological PD, but death recorded on eCRF	Date of death	Event
Neither radiological PD nor death	Date of last radiological assessment	Censored
Subject received new anti-cancer therapy (ACT)*:		
Radiological PD per RECIST v1.1 documented only after start of new ACT	Date of last radiological assessment before start of new ACT	Censored
Radiological PD documented per RECIST v1.1 before start of new ACT	Date of first radiological PD	Event
No radiological PD nor death	Date of last radiological assessment before start of new ACT	Censored
Missed >=2 scheduled radiological assessments:		
If radiological PD or death occurs after missing 2 or more scheduled radiological assessments**	Date of last radiological assessment	Censored

Note: PFS = date of event or censoring - date of randomization + 1. NE will be treated as missing for the derivation described this table. *New ACT includes new anti-cancer surgery, radiotherapy, chemo, immunotherapy (other than zolbetuximab and mFOLFOX6 components), and on study tumour directed procedure. after randomization. If a subject in Arm B switches from placebo to zolbetuximab, it is also considered start of new ACT. **If the first radiological assessment after subject missed >=2 imaging assessments is SD or better and it's confirmed that subject did not take any other ACT during the missing period, the following imaging assessments will be used rather than censored.

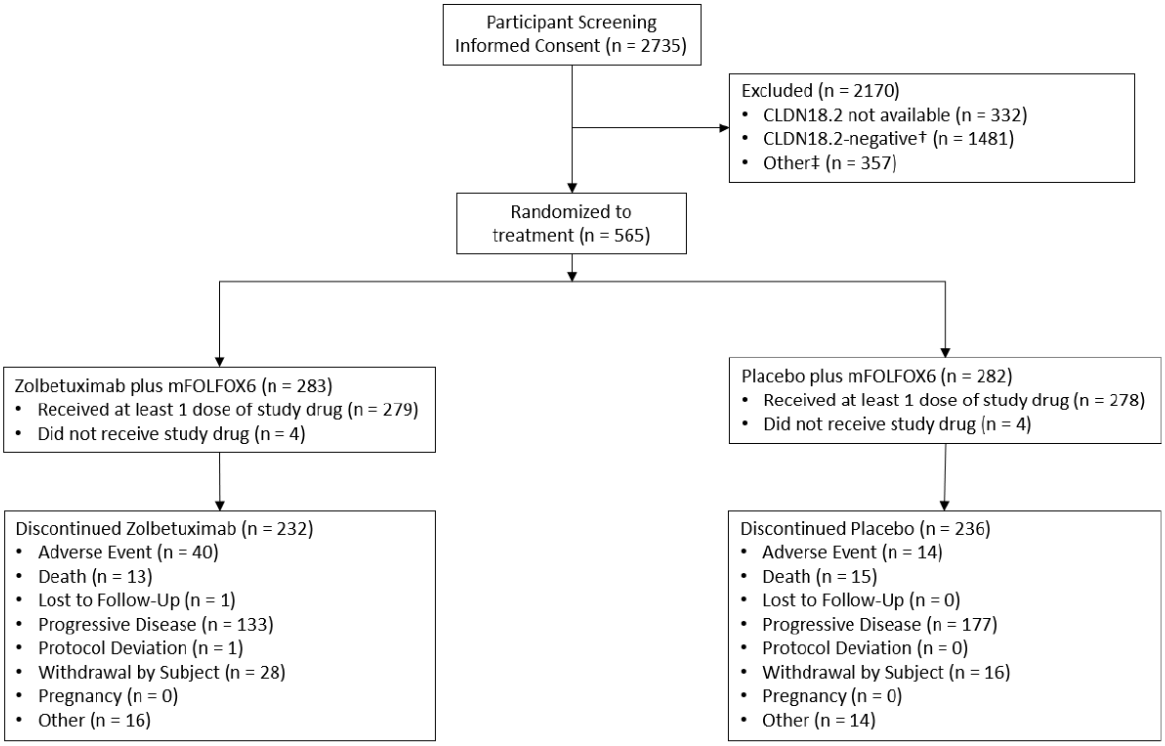
Several sensitivity and subgroup analyses were prespecified. The sensitivity analyses were planned to (SA1) address discrepancies between IRC and local investigator's PD assessment, (SA2) treat likely informative censoring as PFS events and (SA3) address a different censoring of death after new ACT. Missing data imputation was avoided as possible, and addressed via conservative imputation methods in case this was necessary.

No interim analysis for PFS were planned. One interim analysis for OS at time of the primary PFS analysis was planned. PFS was planned to be tested once at 1-sided significance level of 0.025. Only if PFS is significant, was hypothesis testing for OS interim and OS final analyses to be performed. An O'Brien-Fleming type alpha-spending function [Lan & DeMets, 1983] was planned to be utilized to control the overall 1-sided 0.025 significance level for the OS interim and final analyses.

Results

Participant flow

Figure 2: Participant disposition



CLDN18.2 not available was defined as participants for whom valid IHC results were not obtained.

‡ "Other" represents participants whose tumours were CLDN18.2-positive but failed screening for other reasons including withdrawal by participant, laboratory findings, HER2-expression status, and Eastern Cooperative Oncology Group performance-status score.

Table 26: End of Treatment – Zolbetuximab or Placebo (SAF)

Parameter Category	Arm A Zolbetuximab + mFOLFOX6 (n = 279) n (%)	Arm B Placebo + mFOLFOX6 (n = 278) n (%)	Overall (n = 557) n (%)
Zolbetuximab or placebo Discontinuation			
No	47 (16.8)	42 (15.1)	89 (16.0)
Yes	232 (83.2)	236 (84.9)	468 (84.0)
Reason for Discontinuation†			
Adverse event	40 (14.3)	14 (5.0)	54 (9.7)
Death	13 (4.7)	15 (5.4)	28 (5.0)
Lost to follow-up	1 (0.4)	0	1 (0.2)
Progressive disease	133 (47.7)	177 (63.7)	310 (55.7)
Protocol deviation	1 (0.4)	0	1 (0.2)
Withdrawal by participant	28 (10.0)	16 (5.8)	44 (7.9)
Pregnancy	0	0	0
Other	16 (5.7)	14 (5.0)	30 (5.4)
If Progressive Disease or Death‡			
Radiographic progression	101 (36.2)	133 (47.8)	234 (42.0)
Clinical progression	54 (19.4)	74 (26.6)	128 (23.0)

Data cutoff: 09 Sep 2022; SAF: safety analysis set
† Primary study drug treatment discontinuation.
‡ Some participants had both radiographic and clinical progression.

Table 27: End of Treatment – FOLFOX (SAF)

Parameter	Category	Arm A (N=279)	Arm B (N=278)	Overall (N=557)
mFOLFOX6 Discontinuation	No [1]	58 (20.8%)	43 (15.5%)	101 (18.1%)
	Yes	221 (79.2%)	235 (84.5%)	456 (81.9%)
Primary Study Drug Treatment Status	Completed	11 (3.9%)	6 (2.2%)	17 (3.1%)
	Adverse Event	25 (9.0%)	19 (6.8%)	44 (7.9%)
	Death	13 (4.7%)	14 (5.0%)	27 (4.8%)
	Lost to Follow-Up	1 (0.4%)	0	1 (0.2%)
	Progressive Disease	128 (45.9%)	153 (55.0%)	281 (50.4%)
	Protocol Deviation	1 (0.4%)	0	1 (0.2%)
	Withdrawal by Subject	30 (10.8%)	17 (6.1%)	47 (8.4%)
	Pregnancy	0	0	0
	Other	23 (8.2%)	32 (11.5%)	55 (9.9%)

Recruitment

Date of First Participant Screened: 21 Jun 2018

Data Cutoff Date for Present Primary Analysis: 09 Sep 2022

The median follow-up time for the PFS analysis was 12.94 months (95% CI: 11.63, 15.28) in the zolbetuximab plus mFOLFOX6 arm and 12.65 months (95% CI: 10.71, 15.24) in the placebo plus mFOLFOX6 arm. The median follow-up time for the OS analysis was 22.14 months (95% CI 18.04, 24.77) and 20.93 months (19.61, 25.66), respectively.

The study was conducted in 20 countries with 215 sites screening at least one participant. Number of patients enrolled across countries (according to list of randomizations):
Europe: Spain (71), Italy (64), United Kingdom (34), France (29), Belgium (17), Poland (15), Germany (14); North America: United States (n=68), Canada (8); South America: Peru (13), Brazil (12), Mexico (12), Chile (12), Colombia (10); Asia: Japan (65), China (36), Korea (46), Taiwan (30); other: Australia (7), Israel (2).

Conduct of the study

Protocol amendments (excerpts)

Original protocol Version 1.0 (31 Jan 2018)

Version 2.0 (06 Jul 2018) incorporating substantial Amendment 1

Clarifications and changes added mainly related to safety (such as ECG collection prior to every oxaliplatin infusion and monitoring of electrolytes to minimize risk of ventricular arrhythmias; require creatinine clearance ≥ 30 mL/min, modify inclusion crit. to allow single dose of corticosteroids within 14 days prior to first dose, exclude treatment with herbal medications with known antitumor activity, or require screening for dihydropyrimidine dehydrogenase (DPD) deficiency).

Version 3.0 (06 Aug 2019) Incorporating Substantial Amendment 2

- Update of study population to include non-measurable disease
- Allow enrolment of subjects requiring transfusions if they have a post transfusion haemoglobin of ≥9 g/dL.

- Changes introduced to refine eligibility criteria
- Revisions introduced to zolbetuximab treatment modifications (including discontinuation of zolbetuximab/placebo if posterior reversible encephalopathy syndrome [PRES] is suspected).

Version 4.0 (29 Aug 2019) Incorporating China-specific Substantial Amendment 3

Introduced minor changes such as update of CLDN18.2 slide requirement and removal of central analysis of HER2 tumour samples; remove collection and analyses of exploratory biomarker samples, optional PGx and post-progression tumour samples.

Version 5.0 (18 Oct 2021) Incorporating Substantial Amendment 4

- The number of PFS events required for the interim analysis of overall survival is reduced from 344 to 300.
  Rationale: *The number of required PFS events has been adjusted based on the enrolment and event accrual rates to maintain the timing of Primary Analysis with adequate power which is > 93%.*
- Addition of health economics and outcomes research (HEOR) related key secondary endpoints, including physical function, Pain, and Global Health Score.
- Clarify that a subject receiving oxaliplatin should not receive live vaccines.
- The Per Protocol Set (PPS) has been removed from the protocol.

Changes in Planned Analyses

There were no changes in the planned analyses for the study.

TTCD of PF, OG25-Pain, and GHS/QoL (key secondary endpoint) was evaluated based on a threshold obtained from existing literature because the results of exit survey are pending. As the exit survey started after the initiation of the clinical trial, the results are immature to derive the threshold for clinically meaningful deterioration. The CSR will be amended to include analysis of TTCD based on exit survey study results after sufficient data have been accrued.

COVID-19 Impact Summary

The study included the period during which the COVID-19 pandemic occurred. There were 2 significant actions taken during the COVID-19 pandemic to maintain the safety of clinical study participants and delivering continuity of care in the clinical study setting.

- All ongoing and actively recruiting studies conducted by Astellas had screening and randomization temporarily paused during the pandemic (in most countries from Mar 2020 until Apr to Sep 2020 for the study SPOTLIGHT and from Mar 2020 until Apr to Dez 2020 for the study GLOW).
- Alternative study measures to assess safety and efficacy parameters as appropriate for sites impacted by the COVID-19 pandemic or other crises were communicated to sites via a Dear Investigator Letter on 10 Apr 2020 and subsequently added to the study protocol.

Protocol deviations

A major protocol deviation is defined as one that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject.

Table 28: Major Protocol Deviations (SAF)

Deviation Code	Arm A Zolbetuximab + mFOLFOX6 (n = 279)	Arm B Placebo + mFOLFOX6 (n = 278)	Overall (n = 557)
Any deviation, n (%†)	92 (33.0)	61 (21.9)	153 (27.5)
PD1‡	40 (14.3)	33 (11.9)	73 (13.1)
PD2	9 (3.2)	9 (3.2)	18 (3.2)
PD3	55 (19.7)	24 (8.6)	79 (14.2)

PD1: Entered into the study even though they did not satisfy entry criteria.
PD2: Developed withdrawal criteria during the study and was not withdrawn.
PD3: Received wrong treatment or incorrect dose.

PD: protocol deviation; SAF: safety analysis set.
† Deviation code is presented in summary table.
‡ Astellas doesn't allow waivers to eligibility criteria

Major protocol deviations were reported by 33.0% in the zolbetuximab arm and 21.9% in the placebo arm. The difference between treatment arms were mainly due to temperature monitoring devices used during zolbetuximab shipments (Protocol Deviation Category 3). The Applicant confirmed that no temperature excursions occurred on any of the dispensed medication. Other frequent category 3 deviations were related to applying the loading dose of zolbetuximab (800 mg/m²) instead of the maintenance dose of 600 mg/m² or administration of mFOLFOX6 less than 12 days apart. The most frequent violation of eligibility criteria (PD1) were related to Informed Consent Form issues (participants signing a superseded version of the ICF with later re-consenting in most of those patients) and out of range or missing safety labs at the time of participant randomization (with most participants having confirmed within range local or central safety lab results available prior to C1D1 dosing).

Accidently unblinding

With the responses to the D120 LoQ the Applicant provided clinical study report amendments to add information about accidental unblinding incidents in the course of studies SPOTLIGHT and GLOW. These were not previously reported, because "according to Astellas quality documents and processes, incidents of accidental unblinding are classified as potential Good Clinical Practice (GCP) issues, and not part of the protocol deviation categories reportable in the CSR." However, based on a request from the FDA the CSR is being updated to include this information for transparency.

The Applicant reported 21 incidents of unblinding in both studies. 20 incidents involved specific clinical sites and affected 37 patients across both studies. One incident referred to a meeting with the blinded clinical team members and data management members (on 03 Aug 2020), where potential unblinding information were displayed on a shared screen. In addition, the Interactive Response technology (IRT) vendor uploaded documentation to the external data folders containing drug accountability information of both GLOW and SPOTLIGHT studies.

The Applicant evaluated each accidental unblinding incident and considered none of these a serious GCP breach or a significant quality issue (SQI). None of the accidental unblinding incidents resulted in revealing the participant's treatment assignment to the participant or to the independent central radiologists at any time during the trial conduct. Therefore, the Applicant concluded that these unblinding incidents had no impact on the primary or secondary endpoints of the trial and the data integrity.

Baseline data

38.4% of screened participants had tumours that were CLDN18.2 positive (defined as ≥ 75% of tumour cells, demonstrating moderate to strong membranous CLDN18 staining).

Table 29: Demographic Characteristics (FAS)

Parameter Category/Statistic	Arm A Zolbetuximab + mFOLFOX6 (n = 283)	Arm B Placebo + mFOLFOX6 (n = 282)	Overall (n = 565)
Sex, n (%)			
Male	176 (62.2)	175 (62.1)	351 (62.1)
Female	107 (37.8)	107 (37.9)	214 (37.9)
Ethnicity, n (%)			
Hispanic or Latino	36 (13.8)	37 (14.8)	73 (14.3)
Not Hispanic or Latino	225 (86.2)	213 (85.2)	438 (85.7)
Missing	22	32	54
Race, n (%)			
White	140 (53.6)	134 (53.0)	274 (53.3)
Black or African American	5 (1.9)	2 (0.8)	7 (1.4)
Asian	96 (36.8)	97 (38.3)	193 (37.5)
American Indian or Alaska Native	9 (3.4)	8 (3.2)	17 (3.3)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	11 (4.2)	12 (4.7)	23 (4.5)
Missing	22	29	51
Age (Years)			
N	283	282	565
Mean (SD)	59.7 (11.7)	58.8 (13.0)	59.3 (12.4)
Median (min, max)	62.0 (27, 83)	60.0 (20, 86)	61.0 (20, 86)
Age Group 1 (Years), n (%)			
≤65	181 (64.0)	181 (64.2)	362 (64.1)
>65	102 (36.0)	101 (35.8)	203 (35.9)
Age Group 2 (Years), n (%)			
≤75	267 (94.3)	260 (92.2)	527 (93.3)
>75	16 (5.7)	22 (7.8)	38 (6.7)
ECOG Status at Baseline, n (%)			
0	125 (44.8)	115 (41.4)	240 (43.1)
1	153 (54.8)	163 (58.6)	316 (56.7)
2	1 (0.4)	0	1 (0.2)
Missing	4	4	8
Weight (kg)			
N	279	278	557
Mean (SD)	64.66 (14.47)	65.43 (16.39)	65.04 (15.45)
Median (min, max)	63.00 (38.0, 110.6)	64.80 (28.5, 128.3)	63.00 (28.5, 128.3)
Height (cm)			
N	279	277	556
Mean (SD)	167.17 (9.25)	166.87 (10.33)	167.02 (9.79)
Median (min, max)	168.00 (145.0, 188.0)	167.50 (143.0, 196.0)	168.00 (143.0, 196.0)
BMI (kg/m^2)			
N	279	277	556
Mean (SD)	23.19 (4.19)	23.47 (4.55)	23.33 (4.37)
Median (min, max)	22.98 (15.6, 41.8)	23.18 (13.4, 43.1)	22.99 (13.4, 43.1)
BSA (m^2)			
N	279	277	556
Mean (SD)	1.73 (0.23)	1.74 (0.25)	1.74 (0.24)
Median (min, max)	1.73 (1.2, 2.4)	1.73 (1.1, 2.5)	1.73 (1.1, 2.5)
Tobacco History, n (%)			
Never	142 (50.5)	137 (48.9)	279 (49.7)
Current	26 (9.3)	25 (8.9)	51 (9.1)
Former	113 (40.2)	118 (42.1)	231 (41.2)
Missing	2	2	4

Table 30: Primary Diagnosis and Baseline Disease Characteristics (FAS)

Parameter Category/Statistic	Arm A Zolbetuximab + mFOLFOX6 (n = 283)	Arm B Placebo + mFOLFOX6 (n = 282)	Overall (n = 565)
Primary Diagnosis			
Gastric adenocarcinoma	219 (77.4)	210 (74.5)	429 (75.9)
GEJ adenocarcinoma	64 (22.6)	72 (25.5)	136 (24.1)
Duration Since Initial Diagnosis (days)			
N	273	275	548
Mean (SD)	270.4 (478.5)	297.6 (675.2)	284 (585.1)
Median (Min, Max)	56 (2, 3010)	56 (7, 5366)	56 (2, 5266)
Tumor Location			
Gastric			
N	219	210	429
Proximal	73 (33.6)	59 (28.1)	132 (30.9)
Distal	91 (41.9)	87 (41.4)	178 (41.7)
Unknown	53 (24.4)	64 (30.5)	117 (27.4)
Missing	2	0	2
GEJ			
N	64	72	136
Proximal	30 (47.6)	26 (36.6)	56 (41.8)
Distal	19 (30.2)	31 (43.7)	50 (37.3)
Unknown	14 (22.2)	14 (19.7)	28 (20.9)
Missing	1	1	2
Tumor Type			
Diffuse	82 (29.1)	117 (42.1)	199 (35.5)
Intestinal	70 (24.8)	66 (23.7)	136 (24.3)
Mixed	31 (11.0)	13 (4.7)	44 (7.9)
Unknown	49 (17.4)	40 (14.4)	89 (15.9)
Other	50 (17.7)	42 (15.1)	92 (16.4)
Missing	1	4	5
Primary Tumor (T)			
TX	62 (22.1)	46 (16.4)	108 (19.2)
T0	0	0	0
Tis	1 (0.4)	2 (0.7)	3 (0.5)
T1	2 (0.7)	4 (1.4)	6 (1.1)
T1a	2 (0.7)	1 (0.4)	3 (0.5)
T1b	2 (0.7)	6 (2.1)	8 (1.4)
T2	15 (5.3)	16 (5.7)	31 (5.5)
T3	86 (30.6)	98 (34.9)	184 (32.7)
T4	32 (11.4)	35 (12.5)	67 (11.9)
T4a	56 (19.9)	56 (19.9)	112 (19.9)
T4b	23 (8.2)	17 (6.0)	40 (7.1)
Missing	2	1	3

Regional Lymph Nodes (N)			
NX	66 (23.7)	60 (21.4)	126 (22.5)
N0	40 (14.3)	38 (13.6)	78 (14.0)
N1	56 (20.1)	66 (23.6)	122 (21.8)
N2	44 (15.8)	51 (18.2)	95 (17.0)
N3	42 (15.1)	32 (11.4)	74 (13.2)
N3a	17 (6.1)	19 (6.8)	36 (6.4)
N3b	14 (5.0)	14 (5.0)	28 (5.0)
Missing	4	2	6
Distant Metastasis (M)†			
M0	85 (30.4)	70 (24.8)	155 (27.6)
M1	195 (69.6)	212 (75.2)	407 (72.4)
Missing	3	0	3
Tumor Metastatic†			
No	44 (15.5)	44 (15.6)	88 (15.6)
Yes	239 (84.5)	238 (84.4)	477 (84.4)
Metastasis Location (≥5% participants in any treatment group) ‡			
Abdominal cavity	19 (6.7)	17 (6.0)	36 (6.4)
Bone	28 (9.9)	23 (8.2)	51 (9.0)
Liver	62 (21.9)	75 (26.6)	137 (24.2)
Lung	36 (12.7)	33 (11.7)	69 (12.2)
Lymph node	101 (35.7)	109 (38.7)	210 (37.2)
Ovary	16 (5.7)	19 (6.7)	35 (6.2)
Peritoneum	94 (33.2)	76 (27.0)	170 (30.1)
History of H. Pylori Infection			
No	139 (49.1)	136 (48.2)	275 (48.7)
Yes	31 (11.0)	45 (16.0)	76 (13.5)
Unknown	113 (39.9)	101 (35.8)	214 (37.9)
Barrett's Esophagus Diagnosed			
No	166 (58.7)	173 (61.3)	339 (60.0)
Yes	7 (2.5)	11 (3.9)	18 (3.2)
Unknown	110 (38.9)	98 (34.8)	208 (36.8)
CLDN18.2 Testing Result			
<75%	0§	0	0
≥75%	283 (100.0)	282 (100.0)	565 (100.0)
Not applicable	0	0	0
HER2-positive Status	0	0	0
Measurable Disease Based on Central Imaging (Yes)	211 (74.6)	211 (74.8)	422 (74.7)
Measurable Disease Based on Local Imaging (Yes)	235 (83.0)	227 (80.5)	462 (81.8)

† Distant metastases (M1) and tumour metastatic (Y) may differ depending on date of initial diagnosis ("distant metastasis" refers to disease status at initial diagnosis; "tumour metastatic" refers to status at study entry).

‡ Other metastasis locations (reported in < 5% of participants) were omentum (3.9%), retroperitoneum (2.8%), adrenal gland (2.3%), oesophagus (1.2%), mediastinum (1.2%), stomach (1.8%), pleura (1.6%), pancreas (1.1%), chest (0.9%), colon (0.9%), pelvis (0.9%), spleen (0.9%), heart (0.5%), rectum (0.5%), kidney (0.4%), bladder (0.2%), brain (0.2%), breast (0.2%), gallbladder (0.2%), neck (0.2%), pericardium (0.2%), skin (0.2%) and/or other (7.1%).

§ CLDN18.2 testing result is based on testing results generated during screening and prior to randomization. One participant in the zolbetuximab plus mFOLFOX6 arm was randomized based on a positive CLDN18.2 status but was later rescored after randomization (in response to a diagnostic protocol deviation) as CLDN18.2 negative).

Table 31: Stratification factors reported at randomization by IRT

Parameter, n (%)	Arm A (N=283)	Arm B (N=282)	Overall (N=565)
Region=Asia	88 (31.1%)	89 (31.6%)	177 (31.3%)
Region=Non-Asia	195 (68.9%)	193 (68.4%)	388 (68.7%)
Number of Metastatic Sites=0-2	219 (77.4%)	219 (77.7%)	438 (77.5%)
Number of Metastatic Sites=>=3	64 (22.6%)	63 (22.3%)	127 (22.5%)
Prior Gastrectomy=Yes	84 (29.7%)	82 (29.1%)	166 (29.4%)
Prior Gastrectomy=No	199 (70.3%)	200 (70.9%)	399 (70.6%)

Prior and concomitant medication

The frequency of prior and concomitant medication use was overall similar across the treatment groups; however, higher use of concomitant medications in the zolbetuximab arm vs the placebo arm was reported for e.g., antiemetics (70% and 63%), antihistamines (39% vs 29%), anti-inflammatory products, glucocorticoids (41% vs 31%), H2-receptor antagonists (21% vs 9%), and propulsives (70% vs 51%).

Prior anticancer therapy

Overall, 21.1% participants had received prior chemotherapy in the neoadjuvant/adjuvant setting (23.3% in the zolbetuximab arm and 18.8% in the placebo arm). Prior radiation therapy was received by 7.3% participants. Reasons for radiation were primary disease (3.9%), palliation (2.7%) and other (1.1%).

Subsequent anticancer therapies

Table 32: New anticancer therapies (FAS) (most common, excerpt from CSR Table 9.2.2.6.1)

Therapeutic group; n (%) **Chemical group (most common)**	**Arm A** **Zolbetuximab + mFOLFOX6** **(N=283)**	**Arm B** **Placebo mFOLFOX6** **(N=282)**	**Overall (N=565)**
Overall	135 (47.7%)	148 (52.5%)	283 (50.1%)
Antineoplastic agents	133 (47.0%)	141 (50.0%)	274 (48.5%)
Taxanes Paclitaxel	63 (22.3%) 48 (17.0%)	67 (23.8%) 55 (19.5%)	130 (23.0%) 103 (18.2%)
Pyrimidine analagoues	22 (7.8%)	24 (8.5%)	46 (8.1%)
(TOP1 inhibitors) Irinotecan	8 (2.8%)	15 (5.3%)	23 (4.1%)
Platinum compounds	9 (3.2%)	9 (3.2%)	18 (3.2%)
VEGF/VEGFR inhibitors Ramucirumab	35 (12.4%)	34 (12.1%)	69 (12.2%)
VEGFR TKI	1 (0.4%)	2 (0.7%)	3 (0.5%)
PD-1/PDL-1 inhibitors	31 (11.0%)	30 (10.6%)	61 (10.8%)
Nivolumab	18 (6.4%)	22 (7.8%)	40 (7.1%)
Pembrolizumab	8 (2.8%)	6 (2.1%)	14 (2.5%)
Combination of antineoplastic agents	54 (19.1%)	57 (20.2%)	111 (19.6%)

Numbers analysed

Table 33: Analysis Sets (All Randomized Participants)

Analysis Set	Arm A Zolbetuximab + mFOLFOX6 (n = 283) n %	Arm B Placebo + mFOLFOX6 (n = 282) n %	Overall (n = 565) n %
Safety analysis set (SAF)†	279 (98.6)	278 (98.6)	557 (98.6)
Full analysis set (FAS)‡	283 (100.0)	282 (100.0)	565 (100.0)
Pharmacokinetics analysis set§	275 (97.2)	0	275 (48.7)

† All participants who received at least 1 dose of any study drug (zolbetuximab or placebo/mFOLFOX6)
‡ All participants randomized to 1 of the treatment arms.
§ All participants from the safety analysis set for which at least 1 zolbetuximab concentration measurement was available.

Outcomes and estimation

Primary endpoint - **PFS** assessed by IRC

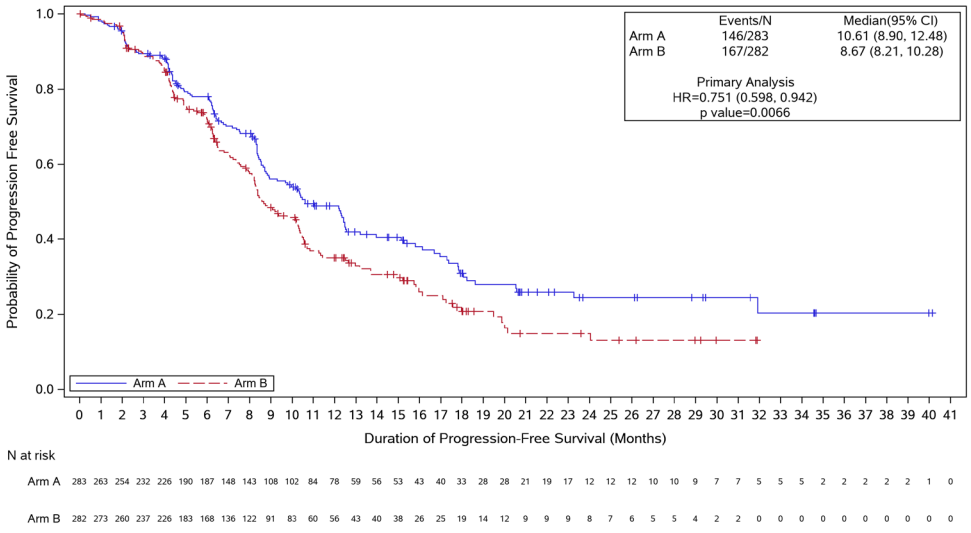
The primary PFS analysis was conducted with 313 PFS events (planned with 300 events) at the data cutoff date of 09 Sep 2022. Treatment with zolbetuximab plus mFOLFOX6 showed a statistically significant improvement in progression-free survival (as assessed by IRC per RECIST v1.1) compared with placebo plus mFOLFOX6 treatment (HR = 0.751, 95% CI: 0.598, 0.942; 1-sided P = 0.0066).

Table 34: PFS assessed by IRC per RECIST v1.1 – FAS (SPOTLIGHT)

Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 283)	Arm B Placebo plus mFOLFOX6 (n = 282)
PFS events, n (%)	146 (51.6)	167 (59.2)
Radiographical progression	87 (30.7)	98 (34.8)
Death without documented progression	59 (20.8)	69 (24.5)
Censored, n (%)	137 (48.4)	115 (40.8)
Duration of PFS (months)†		
Median (95% CI)	**10.61** (8.90, 12.48)	**8.67** (8.21, 10.28)
1st Quartile (95% CI)	6.24 (4.76, 7.20)	5.03 (4.34, 6.21)
3rd Quartile (95% CI)	23.26 (17.84, NE)	16.13 (13.70, 20.01)
Range‡	0.03+, 40.15+	0.03+, 31.90+
Stratified Analysis§		
1-sided P value¶	0.0066	
Hazard ratio (95% CI)††	**0.751 (0.598; 0.942)**	
Median follow-up time (months)‡‡	12.94 (11.63, 15.28)	12.65 (10.71, 15.24)
PFS Rate, % (95% CI)§§		
At 6 months	78.05 (72.43, 82.67)	71.95 (66.03, 77.03)
At 12 months	48.86 (41.92, 55.43)	35.04 (28.45, 41.69)
At 18 months	30.93 (23.83, 38.28)	20.82 (14.48, 27.96)
At 24 months	24.41 (17.36, 32.13)	14.87 (8.78, 22.47)
At 30 months	24.41 (17.36, 32.13)	13.01 (7.07, 20.82)

Data cutoff: 09 Sep 2022.
CI: confidence interval; FAS: full analysis set (= ITT); IRC: independent review committee; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; NE: not estimable; PFS: progression-free survival;
† Based on Kaplan-Meier estimate.
‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology.
¶ Based on 1-sided log-rank test.
†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.
‡‡ Based on reverse Kaplan-Meier estimate.
§§ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Figure 3: Kaplan-Meier Plot of PFS Assessed by IRC – FAS (SPOTLIGHT)



Data cutoff: 09 Sep 2022.

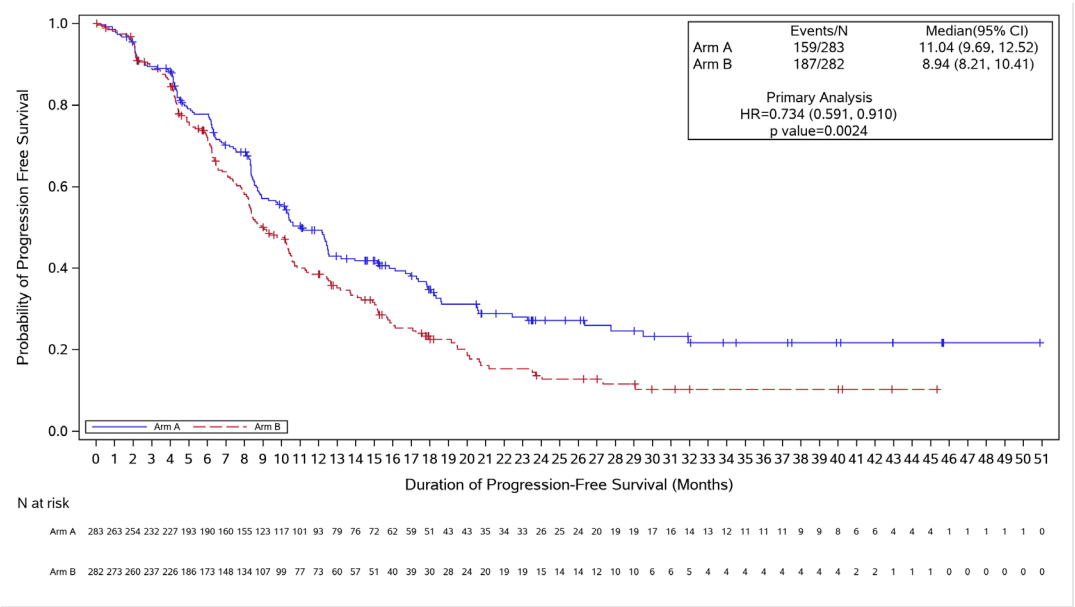
Updated PFS results

Table 35: Updated PFS by IRC per RECIST v1.1 (at the time of final OS analysis, DCO 08 Sep 2023)

Measure	SPOTLIGHT	
	Arm A (N=283)	**Arm B (N=282)**
PFS Events, n (%)	159 (56.2)	187 (66.3)
Radiographical Progression	93 (32.9)	111 (39.4)
Death without Documented Progression	66 (23.3)	76 (27.0)
Censored, n (%)	124 (43.8)	95 (33.7)
Duration of PFS (Months) [1]		
Median (95% CI)	**11.04** (9.69, 12.52)	**8.94** (8.21, 10.41)
Stratified Analysis [3]		
1-sided P-value [4]	0.0024	
HR (95% CI) [5]	**0.734 (0.591, 0.910)**	
Median Follow-Up Time, Months (95% CI) [6]	18.04 (15.28, 23.33)	17.91 (14.78, 23.75)
PFS Rate, % (95% CI) [7]		
At 6 months	77.79 (72.18, 82.41)	72.10 (66.20, 77.15)
At 12 months	49.28 (42.62, 55.60)	38.47 (32.08, 44.81)
At 18 months	34.77 (28.17, 41.44)	22.57 (16.82, 28.85)
At 24 months	27.20 (20.75, 34.03)	13.66 (8.74, 19.66%)
At 42 months	21.74 (15.02, 29.28)	10.30 (5.75, 16.37)
At 48 months	21.74 (15.02, 29.28)	NE (NE, NE)

CI: confidence interval; HR: hazard ratio; NE: non-estimable; PFS: progression-free survival (the time from randomization until death from any cause or radiographic disease progression (per Response Evaluation Criteria in Solid Tumours [RECIST] 1.1), whichever occurs first. In case of no event, PFS is defined using the censoring rules defined in the Statistical Analysis Plan [SAP]).
[1] Based on Kaplan-Meier (KM) estimate.
[2] + indicates censoring.
[3] Stratification factors are Region, Number of Metastatic Sites and Prior Gastrectomy from interactive response technology (IRT).
[4] Based on 1-sided log-rank test.
[5] Based on Cox proportional hazards model with treatment as the only explanatory variable. Assuming proportional hazards, an HR < 1 indicates a reduction in hazard rate in favor of treatment arm.
[6] Based on reverse KM estimate.
[7] PFS rate and 95% CI are estimated using KM method and Greenwood formula.
Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.

Figure 4: Kaplan-Meier Plot of PFS Assessed by IRC (at the time of final OS analysis)



For subgroup analyses, please see Ancillary analyses

Secondary endpoints

OS - key secondary objective

The interim analysis of OS was performed at the time of the final PFS analysis; treatment with zolbetuximab plus mFOLFOX6 resulted in a statistically significant improvement (at a 1-sided significance level of 0.0135) compared with placebo plus mFOLFOX6 treatment (HR = 0.750, 95% CI: 0.601, 0.936; 1-sided P = 0.0053).

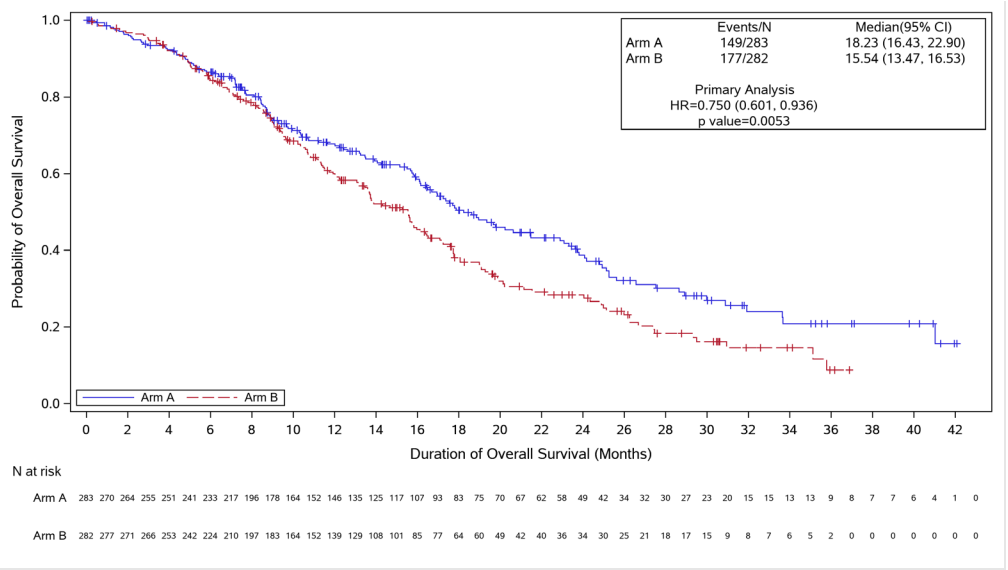
Table 36: Overall Survival – FAS (SPOTLIGHT) – Interim analysis (DCO 09 Sep 2022)

Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 283)	Arm B Placebo plus mFOLFOX6 (n = 282)
Deaths, n (%)	149 (52.7)	177 (62.8)
Censored, n (%)	134 (47.3)	105 (37.2)
Censored at cutoff date, n (%)	19 (6.7)	20 (7.1)
Duration of Overall Survival (months)†		
Median (95% CI)	**18.23** (16.43, 22.90)	**15.54** (13.47, 16.53)
1st Quartile (95% CI)	8.9 (8.11, 10.41)	8.84 (7.23, 9.49)
3rd Quartile (95% CI)	31.93 (25.63, NE)	25.00 (20.14, 29.34)
Range‡	0.03+, 42.09+	0.07, 36.90+
Stratified Analysis§		
1-sided P value¶	0.0053	
Hazard ratio (95% CI)††	**0.750 (0.601, 0.936)**	
Median follow-up time (months)‡‡	22.14 (18.04, 24.77)	20.93 (19.61; 25.66)
Overall Survival Rate, % (95% CI)§§		
At 12 months	67.69 (61.49, 73.12)	59.97 (53.63, 65.72)
At 18 months	50.46 (43.51, 57.00)	38.05 (31.52, 44.54)
At 24 months	38.77 (31.62, 45.85)	28.38 (22.10, 34.98)
At 30 months	26.95 (19.88, 34.51)	16.19 (10.50, 22.97)
At 36 months	20.86 (13.68, 29.08)	8.74 (3.21, 17.79)

Data cutoff: 09 Sep 2022. † Based on Kaplan-Meier estimate. ‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test.

†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm. ‡‡ Based on reverse Kaplan-Meier estimate.
§§ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Figure 5: Kaplan-Meier Plot of Overall Survival – FAS (SPOTLIGHT) - IA



Data cutoff: 09 Sep 2022. P value is generated from stratified 1-sided log-rank test for the comparison of Arm A and Arm B. HR with 95% CI is based on stratified Cox proportional hazard model, with region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.

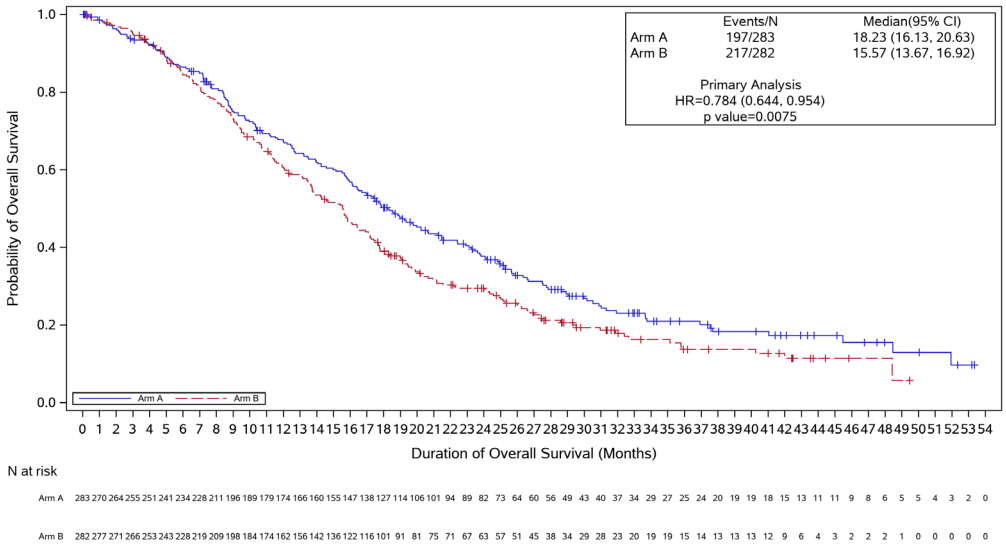
Updated OS results

Table 37: Final OS analysis SPOTLIGHT (data cutoff 08 Sep 2023)

Measure	**SPOTLIGHT**	
	Arm A (N=283)	**Arm B (N=282)**
Deaths, n (%)	197 (69.6)	217 (77.0)
Censored, n (%)	86 (30.4)	65 (23.0)
Censored at Cutoff Date, n (%)	11 (3.9)	13 (4.6)
Duration of OS, Months [1]		
Median (95% CI)	**18.23** (16.13, 20.63)	**15.57** (13.67, 16.92)
1st Quartile (95% CI)	9.03 (8.38, 10.71)	8.71 (7.10, 9.49)
3rd Quartile (95% CI)	30.88 (27.50, 37.68)	26.25 (21.55, 29.50)
Range [2]	0.03+, 53.36+	0.07, 49.48+
Stratified Analysis [3]		
1-sided P-value [4]	0.0075	
HR (95% CI) [5]	**0.784 (0.644, 0.954)**	
Median Follow-Up Time, Months (95% CI) [6]	33.28 (29.27, 37.59)	31.38 (28.68, 36.17)
OS Rate, % (95% CI) [7]		
At 12 months	67.36 (61.36, 72.64)	60.65 (54.57, 66.19)
At 18 months	50.28 (44.07, 56.16)	39.03 (33.17, 44.84)
At 24 months	37.71 (31.68, 43.71)	29.45 (23.99, 35.10)
At 30 months	26.83 (21.17, 32.80)	19.37 (14.50, 24.78)
At 36 months	20.92 (15.53, 26.87)	13.72 (9.12, 19.26)
At 42 months	17.28 (11.99, 23.38)	11.40 (6.89, 17.16)
At 48 months	15.55 (10.07, 22.13)	11.40 (6.89, 17.16)

CI: confidence interval; HR: hazard ratio; NE: non-estimable; OS: overall survival.
Arm A = Zolbetuximab + mFOLFOX6, Arm B = Placebo + mFOLFOX6.
[1] Based on Kaplan-Meier (KM) estimate.
[2] + indicates censoring.
[3] Stratification factors were Region, Number of Metastatic Sites and Prior Gastrectomy from interactive response technology (IRT).
[4] Based on 1-sided log-rank test.
[5] Based on Cox proportional hazards model with treatment as the only explanatory variable. Assuming proportional hazards, an HR < 1 indicates a reduction in hazard rate in favor of treatment arm.
[6] Based on reverse KM estimate.
[7] Survival Rate and 95% CI were estimated using KM method and Greenwood formula.

Figure 6: KM Plot of OS, Study SPOTLIGHT (based on the final Overall Survival Analysis)



For subgroup analyses, please see Ancillary analyses

TTCD (time to first confirmed deterioration) – ("key") secondary objective

TTCD, defined as time to confirmed deterioration using the physical functioning (PF), abdominal pain and discomfort (OG25-Pain) and GHS/QoL scores (as measured by EORTC QLQ-C30 and QLQ-OG25), was another key secondary efficacy endpoint. The threshold values of 13 for Physical Functioning and GHS/QoL are based on [Cocks et al, 2012] and the threshold value of 16.7 for OG25-Pain is based on [Norman et al, 2003] and [Sloan et al, 2005].

A similar median TTCD was observed in the 2 arms. TTCD statistical testing is pending (please see "Changes in Planned Analyses").

Table 38: TTCD for Physical Functioning, OG25-Pain and GHS/QoL (Primary Thresholds, Excluding Death) – FAS (SPOTLIGHT) (excerpt)

Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 283)	Arm B Placebo plus mFOLFOX6 (n = 282)
Physical Functioning (Deterioration Threshold = 13†)		
Total number of participants, n (%)	283 (100.0)	282 (100.0)
Deterioration events, n (%)	115 (40.6)	102 (36.2)
Censored, n (%)	168 (59.4)	180 (63.8)
Time to First Confirmed Physical Functioning Deterioration (months)‡		
Median (95% CI)	**10.71** (6.01, NE)	**12.32** (9.26, NE)

Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 283)	Arm B Placebo plus mFOLFOX6 (n = 282)
Stratified analysis§		
1-sided P value¶	0.0252	
Hazard ratio (95% CI) ††	**1.309 (1.000, 1.713)**	
OG25-Pain (Deterioration Threshold = 16.7†)		
Total number of participants, n (%)	283 (100.0)	282 (100.0)
Deterioration events, n (%)	38 (13.4)	54 (19.1)
Censored, n (%)	245 (86.6)	228 (80.9)
Time to First Confirmed OG25-Pain Deterioration (months)‡		
Median (95% CI)	NYR	NYR (15.08, NE)
Stratified analysis§		
1-sided P value¶	0.0345	
Hazard ratio (95% CI) ††	**0.679 (0.446, 1.034)**	
GHS/QoL (Deterioration Threshold = 13†)		
Total number of participants, n (%)	283 (100.0)	282 (100.0)
Deterioration events, n (%)	111 (39.2)	105 (37.2)
Censored, n (%)	172 (60.8)	177 (62.8)
Time to First Confirmed GHS/QoL Deterioration (months)‡		
Median (95% CI)	**15.44** (6.90, 22.83)	**11.83** (8.74, 15.08)
Stratified analysis§		
1-sided P value¶	0.1321	
Hazard ratio (95% CI) ††	**1.168 (0.890, 1.533)**	

Data cutoff: 09 Sep 2022. NE: not estimable; NYR: not yet reached;

† The threshold values of 13 for Physical Functioning and GHS/QoL are based on [Cocks et al, 2012] and the threshold value of 16.7 for OG25-Pain is based on [Norman et al, 2003] and [Sloan et al, 2005].
‡ Time to confirmed deterioration = date of first confirmed clinically meaningful deterioration/censored date – randomization date + 1.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. ¶ Based on 1-sided log-rank test.
†† Based on stratified Cox proportional hazard model with region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

ORR

Table 39: ORR and DCR Assessed by IRC – Unconfirmed Responses (FAS SPOTLIGHT) (DCO 08 Sep 2023)

Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 283)	Arm B Placebo plus mFOLFOX6 (n = 282)
Best Overall Response, n (%)†	256 (90.5)	266 (94.3)
CR	21 (7.4)	13 (4.6)
PR	115 (40.6)	121 (42.9)
Stable disease	44 (15.5)	51 (18.1)
Non-CR/non-progressive disease	52 (18.4)	60 (21.3)
Progressive disease	15 (5.3)	17 (6.0)
Not evaluable	4 (1.4)	3 (1.1)
No disease	5 (1.8)	1 (0.4)
Not available‡	27	16
ORR, n (%)	136 (**48.1**)	134 (**47.5**)
95% CI for ORR (%)§	(42.11, 54.05)	(41.56, 53.52)
Stratified 1-sided P value¶	0.4536	
DCR, n (%)††	232 (**82.0**)	245 (**86.9**)
95% CI for DCR (%)§	(77.00, 86.28)	(82.37, 90.59)
Stratified 1-sided P value¶	0.0569	

CR: complete response; DCR: disease control rate; ORR: objective response rate; PR: partial response;

† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) was believed to be best response, the assessment should have been at least 8 weeks after randomization. For calculation of percentages, the denominator included the total number of participants in each arm.

‡ No post baseline imaging assessment.

§ Using exact method based on binomial distribution (Clopper-Pearson).

DOR

Table 40: Duration of Response Assessed by IRC –Unconfirmed Responses (FAS)

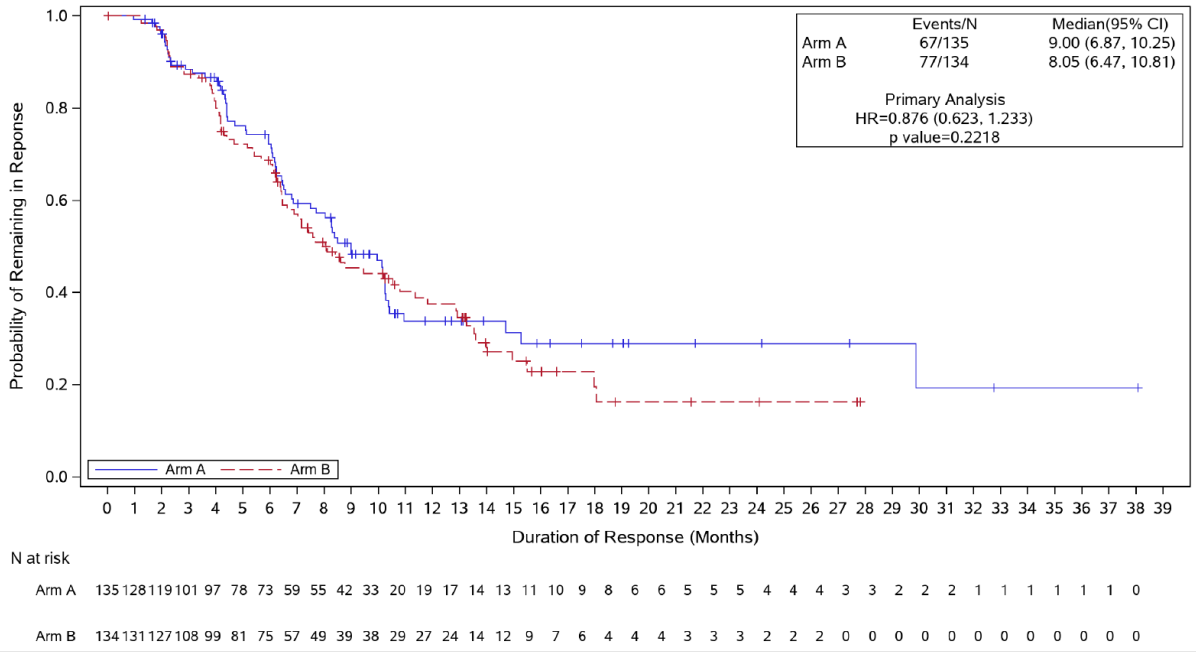
Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n = 135)	Arm B Placebo plus mFOLFOX6 (n = 134)
Events, n (%)	67 (49.6)	77 (57.5)
Censored, n (%)	68 (50.4)	57 (42.5)
Duration of Response (months)†		
Median (95% CI)	**9.00** (6.87, 10.25)	**8.05** (6.47, 10.81)
1st Quartile (95% CI)	5.13 (4.27, 6.24)	4.17 (3.94, 6.11)
3rd Quartile (95% CI)	29.86 (10.94, NE)	15.51 (13.27, NE)
Range‡	0.03+, 38.08+	0.03+, 27.83+
Stratified Analysis§		
1-sided P value¶	0.2218	
Hazard ratio (95% CI)††	**0.876** (0.623, 1.233)	

Data cutoff: 09 Sep 2022. † Based on Kaplan-Meier estimate. ‡ + indicates censoring.

§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test

†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.

Figure 7: KM Plot of DOR, by IRC, unconfirmed responses, FAS



HRQoL

The secondary HRQoL endpoints collected via the EORTC QLQ-C30 and EORTC QLQ-OG25 and EQ-5D-5L were analysed with summary of change from baseline over time through the end of mFOLFOX6 treatment and inferential methods. The compliance rate for completion of the PRO instruments was similar between the treatment arms during the treatment and follow-up periods. Baseline total scores and subscale scores were comparable between treatment arms. The CIs of the total and subscale mean scores overlapped between the treatment groups for most visits during the treatment and follow-up periods though no formal statistical testing was performed on these descriptive summary measures.

Exploratory endpoints

Time to progression - TTP

TTP was defined as the time from the date of randomization to the date of progressive disease as assessed by the IRC per RECIST v1.1.

Table 41: Kaplan-Meier Estimate of TTP Assessed by IRC (FAS) (excerpt)

Parameter	Arm A Zolbetuximab + mFOLFOX6 (n = 283)	Arm B Placebo + mFOLFOX6 (n = 282)
Progression Events, n (%)	87 (30.7)	98 (34.8)
Radiographical progression, n (%)	87 (30.7)	98 (34.8)
Censored, n (%)	196 (69.3)	184 (65.2)
TTP, Months†		
Median (95% CI)	17.81 (12.48, 23.26)	12.52 (10.22, 17.97)
Stratified Analysis§		
1-sided P value¶	0.0133	

Deaths were not included as events. For deaths without documented progressive disease (by the IRC), participants were censored at the time of the last evaluable radiological assessment.
† Based on Kaplan-Meier estimate. ‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from IRT.
¶ Based on 1-sided log-rank test

PFS2

PFS2 was defined as the time from the date of randomization until the date of radiological/objective progressive disease (per participant's local physician) following subsequent (second-line) anticancer therapy (ACT) or death from any cause, whichever was earliest. In cases where PFS2 could not be reliably determined, end date of subsequent (second-line) ACT or start date of third-line ACT was used as the event date. Otherwise, participants were censored.

Table 42: Summary of PFS After Subsequent Therapy, by Investigator Assessment (FAS)

Parameter	Arm A Zolbetuximab + mFOLFOX6 (n = 283)	Arm B Placebo + mFOLFOX6 (n = 282)
PFS2 Events, n (%)	185 (65.4)	203 (72.0)
Progression of disease after new ACT	79 (27.9)	71 (25.2)
Death after new ACT	29 (10.2)	46 (16.3)
Death from any cause without new ACT	64 (22.6)	71 (25.2)
No PD, no death, ended second- or started 3rd line ACT	13 (4.6)	15 (5.3)
Censored, n (%)	98 (34.6)	79 (28.0)
Duration of PFS2, Months†		
Median (95% CI)	14.23 (12.12, 16.82)	11.99 (11.20, 13.40)
1st quartile (95% CI)	8.21 (7.13, 8.77)	7.39 (6.51, 8.48)
3rd quartile (95% CI)	23.72 (19.78, 25.82)	18.07 (15.84, 21.16)
Range ‡	0.03+, 42.09	0.07, 35.78
Stratified Analysis§		
1-sided P value¶	0.0095	
Hazard ratio (95% CI)††	0.782 (0.637, 0.961)	

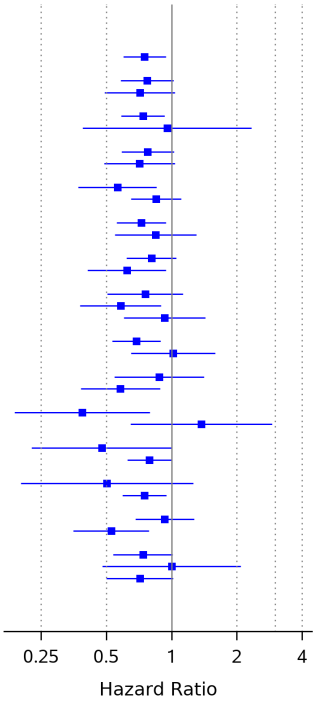
† Based on Kaplan-Meier estimate.
‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from IRT.
¶ Based on 1-sided log-rank test
†† Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favour of the treatment arm.

Ancillary analyses

- **Subgroup analyses** (based on primary analyses)

Figure 8: Forest Plot for Subgroup Analysis of PFS Assessed by IRC – FAS (SPOTLIGHT)

Subgroup	Arm A Event/N	Arm B Event/N	HR [95%CI]
All Subjects	146/283	167/282	0.751 (0.598, 0.942)
Age Group 1: <=65 years	94/181	106/181	0.771 (0.583, 1.019)
>65 years	52/102	61/101	0.714 (0.492, 1.038)
Age Group 2: <=75 years	138/267	154/260	0.739 (0.586, 0.931)
>75 years	8/16	13/22	0.955 (0.390, 2.342)
Sex: Male	95/176	106/175	0.776 (0.587, 1.024)
Female	51/107	61/107	0.711 (0.488, 1.034)
Region: Asia	45/88	47/89	0.563 (0.372, 0.852)
Non-Asia	101/195	120/193	0.848 (0.650, 1.106)
Number of Metastatic Sites: 0-2	107/219	123/219	0.726 (0.559, 0.943)
>=3	39/64	44/63	0.844 (0.548, 1.301)
Prior Gastrectomy: No	106/199	117/200	0.808 (0.620, 1.053)
Yes	40/84	50/82	0.622 (0.410, 0.943)
Tumor Type: Diffuse	40/82	64/117	0.756 (0.506, 1.129)
Intestinal	41/70	46/66	0.582 (0.379, 0.894)
Mixed/Other	49/81	35/55	0.929 (0.601, 1.434)
Medical Condition: Gastric	109/219	126/210	0.688 (0.531, 0.890)
GEJ	37/64	41/72	1.015 (0.649, 1.586)
Gastric Tumor Location: Proximal	40/73	31/59	0.876 (0.545, 1.409)
Distal	39/91	50/87	0.581 (0.381, 0.885)
GEJ Tumor Location: Proximal	14/30	20/26	0.387 (0.189, 0.794)
Distal	12/19	16/31	1.369 (0.646, 2.903)
Country: Japan	12/32	17/33	0.477 (0.226, 1.007)
Non-Japan	134/251	150/249	0.790 (0.625, 0.999)
China	12/19	10/17	0.504 (0.202, 1.258)
Non-China	134/264	157/265	0.750 (0.595, 0.946)
Race: White	77/140	82/134	0.930 (0.681, 1.271)
Asian	47/96	51/97	0.527 (0.352, 0.788)
Tobacco History: Never	75/142	82/137	0.737 (0.538, 1.011)
Current	15/26	14/25	1.001 (0.480, 2.086)
Former	56/113	70/118	0.714 (0.501, 1.018)

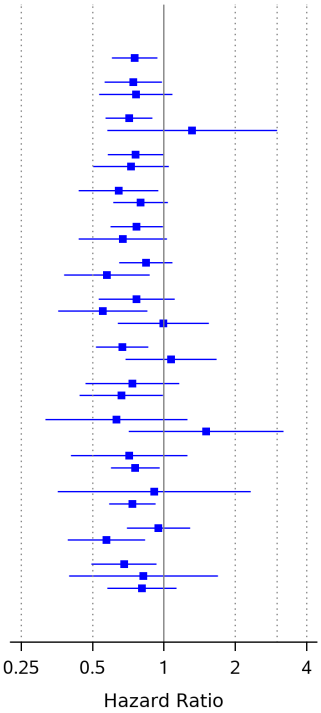


Data cutoff: 09 Sep 2022.

In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favour of the treatment arm. The HR reported for all participants was based on stratified analysis.

Figure 9: Forest Plot for Subgroup Analysis of Overall Survival – FAS (SPOTLIGHT)

Subgroup	Arm A Event/N	Arm B Event/N	HR [95%CI]
All Subjects	149/283	177/282	0.750 (0.601, 0.936)
Age Group 1: <=65 years	89/181	112/181	0.741 (0.561, 0.980)
>65 years	60/102	65/101	0.761 (0.533, 1.086)
Age Group 2: <=75 years	138/267	165/260	0.713 (0.568, 0.895)
>75 years	11/16	12/22	1.315 (0.578, 2.996)
Sex: Male	98/176	113/175	0.760 (0.579, 0.999)
Female	51/107	64/107	0.726 (0.502, 1.049)
Region: Asia	47/88	59/89	0.643 (0.437, 0.947)
Non-Asia	102/195	118/193	0.796 (0.610, 1.039)
Number of Metastatic Sites: 0-2	110/219	129/219	0.767 (0.594, 0.990)
>=3	39/64	48/63	0.670 (0.436, 1.030)
Prior Gastrectomy: No	109/199	125/200	0.839 (0.648, 1.086)
Yes	40/84	52/82	0.575 (0.380, 0.869)
Tumor Type: Diffuse	46/82	75/117	0.766 (0.530, 1.108)
Intestinal	38/70	48/66	0.552 (0.358, 0.851)
Mixed/Other	48/81	34/55	0.992 (0.638, 1.543)
Medical Condition: Gastric	111/219	135/210	0.666 (0.517, 0.858)
GEJ	38/64	42/72	1.072 (0.690, 1.666)
Gastric Tumor Location: Proximal	40/73	37/59	0.736 (0.467, 1.158)
Distal	43/91	53/87	0.660 (0.441, 0.989)
GEJ Tumor Location: Proximal	16/30	18/26	0.629 (0.316, 1.255)
Distal	12/19	16/31	1.505 (0.710, 3.191)
Country: Japan	23/32	27/33	0.713 (0.406, 1.254)
Non-Japan	126/251	150/249	0.757 (0.596, 0.960)
China	9/19	9/17	0.910 (0.357, 2.322)
Non-China	140/264	168/265	0.735 (0.587, 0.922)
Race: White	81/140	81/134	0.948 (0.696, 1.291)
Asian	49/96	65/97	0.572 (0.393, 0.832)
Tobacco History: Never	70/142	87/137	0.678 (0.494, 0.930)
Current	15/26	15/25	0.819 (0.398, 1.686)
Former	64/113	74/118	0.807 (0.576, 1.131)



Data cutoff: 09 Sep 2022.
In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. The HR reported for all participants was based on stratified analysis.

Table 43: Subgroup analysis of ORR, by IRF, unconfirmed responses, FAS No (Data cutoff 08 Sep 2023)

		Arm A			Arm B				
Parameter	Value	N	Events (%)	Median (Months)	N	Events (%)	Median (Months)	Hazard Ratio (HR) 95% CI [1]	P-value [2]
All [3]	-	283	159 (56.2%)	11.04	282	187 (66.3%)	8.94	0.734 (0.591, 0.910)	0.0024
Age Group 1	<=65 years	181	102 (56.4%)	12.19	181	118 (65.2%)	10.15	0.763 (0.585, 0.996)	0.0230
	>65 years	102	57 (55.9%)	10.61	101	69 (68.3%)	8.67	0.681 (0.479, 0.970)	0.0158
Age Group 2	<=75 years	267	151 (56.6%)	11.17	260	169 (65.0%)	8.57	0.739 (0.593, 0.921)	0.0034
	>75 years	16	8 (50.0%)	9.69	22	18 (81.8%)	10.55	0.702 (0.303, 1.625)	0.1992
Sex	Male	176	103 (58.5%)	10.61	175	123 (70.3%)	9.20	0.712 (0.547, 0.926)	0.0054
	Female	107	56 (52.3%)	11.04	107	64 (59.8%)	8.48	0.774 (0.540, 1.110)	0.0807
Region	Asia	88	45 (51.1%)	13.21	89	49 (55.1%)	8.25	0.553 (0.367, 0.833)	0.0021
	Non-Asia	195	114 (58.5%)	10.22	193	138 (71.5%)	10.15	0.814 (0.635, 1.044)	0.0514
Number of Metastatic Sites	0-2	219	119 (54.3%)	12.42	219	140 (63.9%)	10.22	0.712 (0.557, 0.910)	0.0032
	>=3	64	40 (62.5%)	8.21	63	47 (74.6%)	7.98	0.802 (0.525, 1.225)	0.1521
Prior Gastrectomy	No	199	116 (58.3%)	10.18	200	129 (64.5%)	8.74	0.819 (0.636, 1.053)	0.0591
	Yes	84	43 (51.2%)	12.42	82	58 (70.7%)	9.26	0.567 (0.381, 0.842)	0.0022
Tumor Type	Diffuse	82	45 (54.9%)	12.48	117	68 (58.1%)	10.38	0.794 (0.543, 1.160)	0.1156
	Intestinal	70	44 (62.9%)	10.38	66	49 (74.2%)	7.36	0.599 (0.395, 0.909)	0.0073
	Mixed/Other	81	51 (63.0%)	9.79	55	42 (76.4%)	8.67	0.848 (0.563, 1.278)	0.2155
Medical Condition	Gastric	219	118 (53.9%)	12.35	210	138 (65.7%)	8.67	0.660 (0.515, 0.845)	0.0005
	GEJ	64	41 (64.1%)	8.71	72	49 (68.1%)	9.76	1.052 (0.694, 1.594)	0.4060

Gastric Tumor Location	Proximal	73	41 (56.2%)	10.22	59	36 (61.0%)	8.28	0.786 (0.500, 1.234)	0.1463
	Distal	91	45 (49.5%)	15.15	87	55 (63.2%)	9.36	0.546 (0.366, 0.813)	0.0012
GEJ Tumor Location	Proximal	30	18 (60.0%)	11.17	26	21 (80.8%)	7.36	0.553 (0.292, 1.048)	0.0331
	Distal	19	12 (63.2%)	8.77	31	21 (67.7%)	10.84	1.129 (0.554, 2.299)	0.3690
Country	Japan	32	12 (37.5%)	18.07	33	17 (51.5%)	8.28	0.477 (0.226, 1.007)	0.0235
	Non-Japan	251	147 (58.6%)	10.48	249	170 (68.3%)	9.26	0.764 (0.612, 0.953)	0.0083
	China	19	12 (63.2%)	8.54	17	10 (58.8%)	6.24	0.504 (0.202, 1.258)	0.0668
	Non-China	264	147 (55.7%)	12.19	265	177 (66.8%)	9.36	0.732 (0.587, 0.911)	0.0026
Race	White	140	87 (62.1%)	9.30	134	98 (73.1%)	10.22	0.872 (0.653, 1.164)	0.1755
	Asian	96	48 (50.0%)	13.96	97	53 (54.6%)	8.21	0.526 (0.354, 0.781)	0.0006
Tobacco History	Never	142	82 (57.7%)	10.38	137	92 (67.2%)	8.31	0.750 (0.556, 1.011)	0.0289
	Current	26	16 (61.5%)	12.19	25	16 (64.0%)	10.22	0.822 (0.405, 1.670)	0.2964
	Former	113	61 (54.0%)	12.32	118	78 (66.1%)	10.15	0.694 (0.495, 0.972)	0.0159

- **Sensitivity analyses**

Sensitivity analyses of PFS based on primary PFS analysis

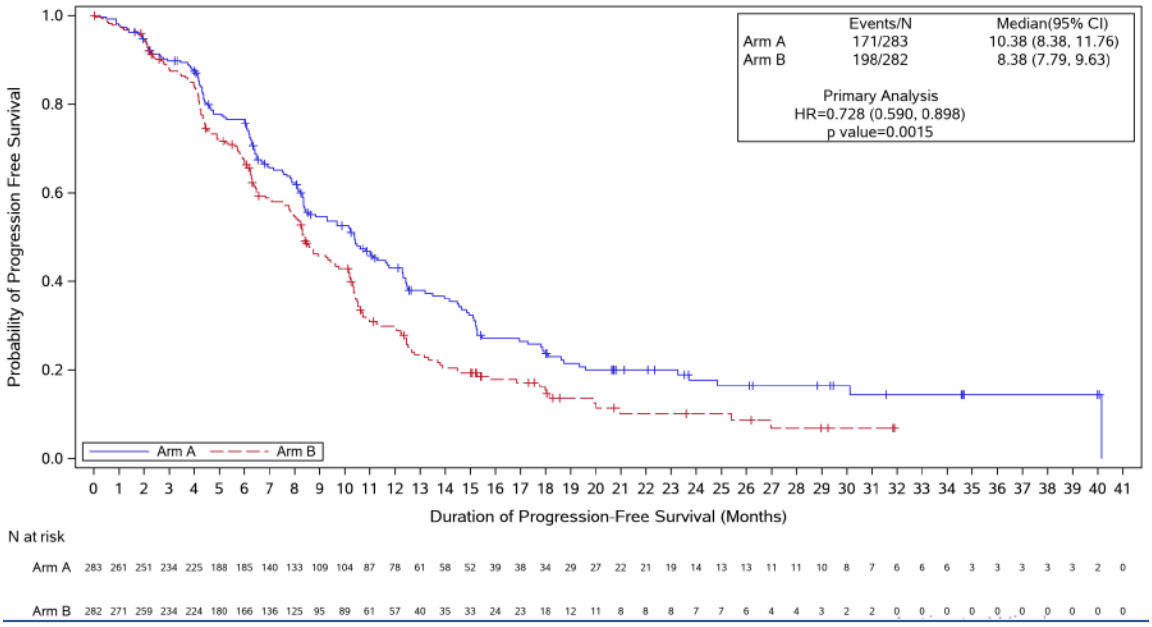
Prespecified sensitivity analysis of PFS were conducted based on investigator assessments, an analysis of the discordance between the IRC and investigator assessments, and a PFS analysis based on informative censoring criteria. For PFS Primary Analysis Definition, please see section statistical methods.

Table 44: Sensitivity analyses of PFS, predefined (assessor´s table from CSR, Tables 13, 14 and 9.3.1.2.2)

Sensitivity analyses of PFS	**HR (95% CI) Nominal P**	**Arm A, Median PFS, Months (95% CI)**	**Arm B, Median PFS, Months (95% CI)**
1) PFS by investigator assessment	**0.728** (0.590, 0.898) 0.0015	10.4 (8.4, 11.8)	8.4 (7.8, 9.6)
2) analysis that treats likely informative censoring as PFS events (analysis included various defined events as PFS events rather than censoring [by IRC assessment]): *radiographical progression as assessed by the investigator, clinical progression as assessed by the investigator, worsening of the ECOG performance status, participants receiving a new ACT, participants with clinical progression or worsening of ECOG performance status and missing ≥2 imaging assessments* Note: radiological PD by IRC and death were also included as events	**0.771** (0.64, 0.93) 0.0038	8.5 (8.2, 10.3)	7.6 (6.5, 8.3)
3) censoring of death after new ATC at date of last radiological assessment before start of new ATC (by IRC)	**0.804** (0.630, 1.026) 0.0391	12.3 (10.2, 15.2)	9.4 (8.3, 10.6)
Primary analysis (for comparison)	**0.751** (0.589, 0.942) 0.0066	10.6 (8.9, 12.5)	8.7 (8.2, 10.3)

ACT: anticancer therapy

Figure 10: Kaplan-Meier Plot of PFS by Investigator Assessment – FAS (SPOTLIGHT)



Data cutoff: 09 Sep 2022

Discordance between IRC and local investigator

Table 45: Discordance between IRC and Local Investigator in PFS Status or Date for Subjects with Measurable Disease (source: CSR Table 9.3.1.2.2)

Variable	Arm A (N=283)	Arm B (N=282)
Overall Disagreement (Either PFS Status or Date), n (%) [1]	97 (34.3%)	116 (41.1%)
Disagreement on PFS Status, n (%)	37 (13.1%)	47 (16.7%)
IRC Event, INV No Event	6 (2.1%)	8 (2.8%)
IRC No Event, INV Event	31 (11.0%)	39 (13.8%)
Disagreement on PFS Event date, n (%) [1]	55 (19.4%)	66 (23.4%)
IRC event date earlier than INV event date	30 (10.6%)	30 (10.6%)
IRC event date later than INV event date	25 (8.8%)	36 (12.8%)
Disagreement on PFS censoring date, n (%) [1]	5 (1.8%)	3 (1.1%)
IRC censoring date earlier than INV censoring date	2 (0.7%)	0
IRC censoring date later than INV censoring date	3 (1.1%)	3 (1.1%)

Sensitivity analyses of ORR

Table 46: Sensitivity analyses for ORR, Assessor´s table, excerpt from Tables 9.3.3.2, 9.3.3.3.2, 9.3.3.3.3, 9.3.3.1

Sensitivity analysis	Parameter	Arm A Zolbetuximab plus mFOLFOX6 (n=283)	Arm B Placebo plus mFOLFOX6 (n=282)
ORR by **ICR, confirmed** responses	ORR %	**40.3**	**39.7**
	(95% CI)	(34.5, 46.3)	(33.96, 45.7)
ORR by **investigator**, **unconfirmed** responses	ORR, n (%)	**53.0**	**44.0**
	(95% CI)	(47.0, 58.9)	(38.1, 49.98)
ORR by **investigator, confirmed** responses	ORR, n (%)	**42.8**	**35.1**
	(95% CI)	(36.9, 48.8)	(29.5, 40.99)
ORR by **ICR, unconfirmed** responses, subjects with **measurable** disease	ORR %	**60.7**	**31.2**
	(95% CI)	(53.7, 67.3)	(55.2, 68.7)

Sensitivity analyses for DOR

Table 47: Sensitivity analyses for DOR, Ass. table, excerpt from Tables 9.3.4.2.1, 9.3.4.2.3, 9.3.4.2.4

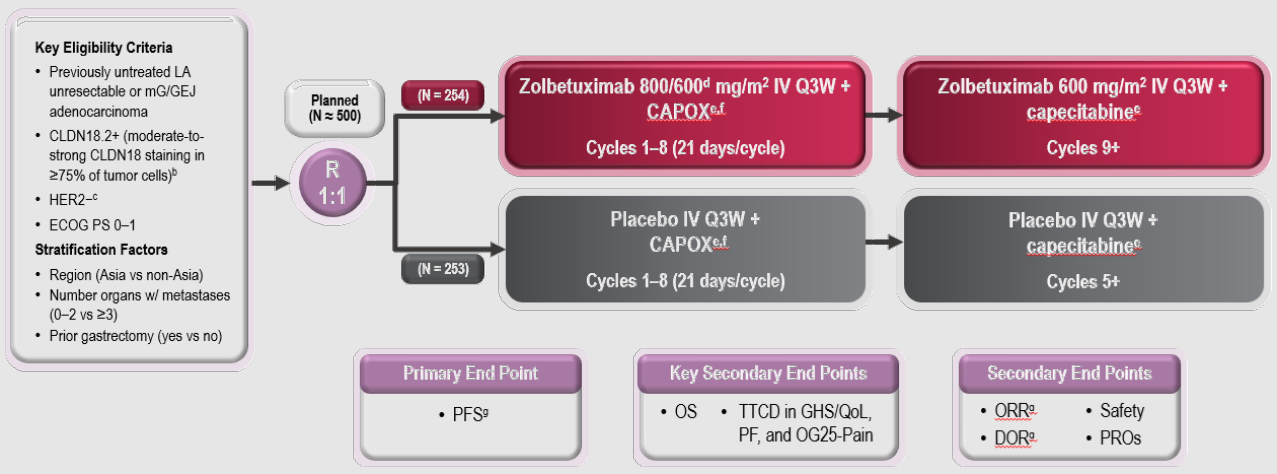
Sensitivity analysis	Parameter	Arm A Zolbetuximab plus mFOLFOX6	Arm B Placebo plus mFOLFOX6
DOR based on **confirmed responses** by **ICR**	**DOR (months)**	N=114	N=112
	Median (95% CI)	10.25 (8.31, 10.94))	10.55 (7.69, 13.27)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.878 (0.592, 1.301)	
DOR based on **investigator** assessment, **confirmed** responses	**DOR (months)**	N=121	N=99
	Median (95% CI)	10.18 (8.87, 12.52)	8.31 (6.80, 9.86)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.680 (0.479, 0.966)	
DOR based on **investigator** assessment, **unconfirmed** responses	**DOR (months)**	N=150	N=124
	Median (95% CI)	9.00 (7.49, 10.25)	6.80 (6.21, 8.31)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.724 (0.534, 0.981)	

2.6.5.3. Main study GLOW

Title: A Phase 3, Global, Multicenter, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared with Placebo Plus CAPOX as First-line Treatment of Subjects with Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (8951-CL-0302)

Methods

Figure 11: GLOW Study Design



Apart from the different chemotherapy backbone regimen, the study design of GLOW was the same as for study SPOTLIGHT.

Study Participants

Same as for study SPOTLIGHT, with the exception of one additional exclusion criteria:

- Subjects has received treatment with herbal medications or other treatments that have known antitumor activity (only in GLOW study).

Treatments

Arm A received zolbetuximab and CAPOX; Arm B received placebo and CAPOX.

Zolbetuximab was administered intravenously as an 800 mg/m² loading dose followed by subsequent doses of 600 mg/m² every 3 weeks (infusion for minimum of 2 hours) [same as for study SPOTLIGHT].

CAPOX was administered as intravenous oxaliplatin 130 mg/m² (infusion for minimum of 2 hours) and capecitabine oral tablets twice daily at a dose of 1000 mg/m². Oxaliplatin was administered on Day 1 of each 21-day cycle (every 3 weeks); capecitabine was administered twice daily on Days 1-14 of each 21-day cycle. Participants received up to 8 CAPOX treatments. After a maximum of 8 treatments of oxaliplatin, participants could continue to receive capecitabine at the investigator's discretion until the participant met study treatment discontinuation criteria.

Antiemetic premedication and dose modification recommendation for zolbetuximab are identical as for Study SPOTLIGHT.

Objectives/endpoints

Objectives/endpoints are identical for both pivotal studies, apart from the addition of STO22 Belching subscale for the evaluation of PROs in study GLOW.

Sample size

500 participants were planned to be recruited in order to collect 300 PFS events and 386 OS events. The planned 300 PFS events during the study will provide 93.4% power to detect a difference in PFS between Arm A (Zolbetuximab + CAPOX) with the assumption of 9 months median PFS time and Arm B (placebo + CAPOX) with the assumption of 6 months median PFS time (hazard ratio = 0.67) at the overall 1-sided 0.025 significance level. Similarly, the planned 386 OS events during the study will

provide 80% power to detect a difference in OS between Arm A (Zolbetuximab + CAPOX) with the assumption of 14.7 months median OS time and Arm B (placebo + CAPOX) with the assumption of 11 months median OS time (hazard ratio = 0.75) at the overall 1-sided 0.025 significance level.

Randomisation and blinding (masking)

Randomisation and blinding were defined exactly as in the SPOTLIGHT study, see above.

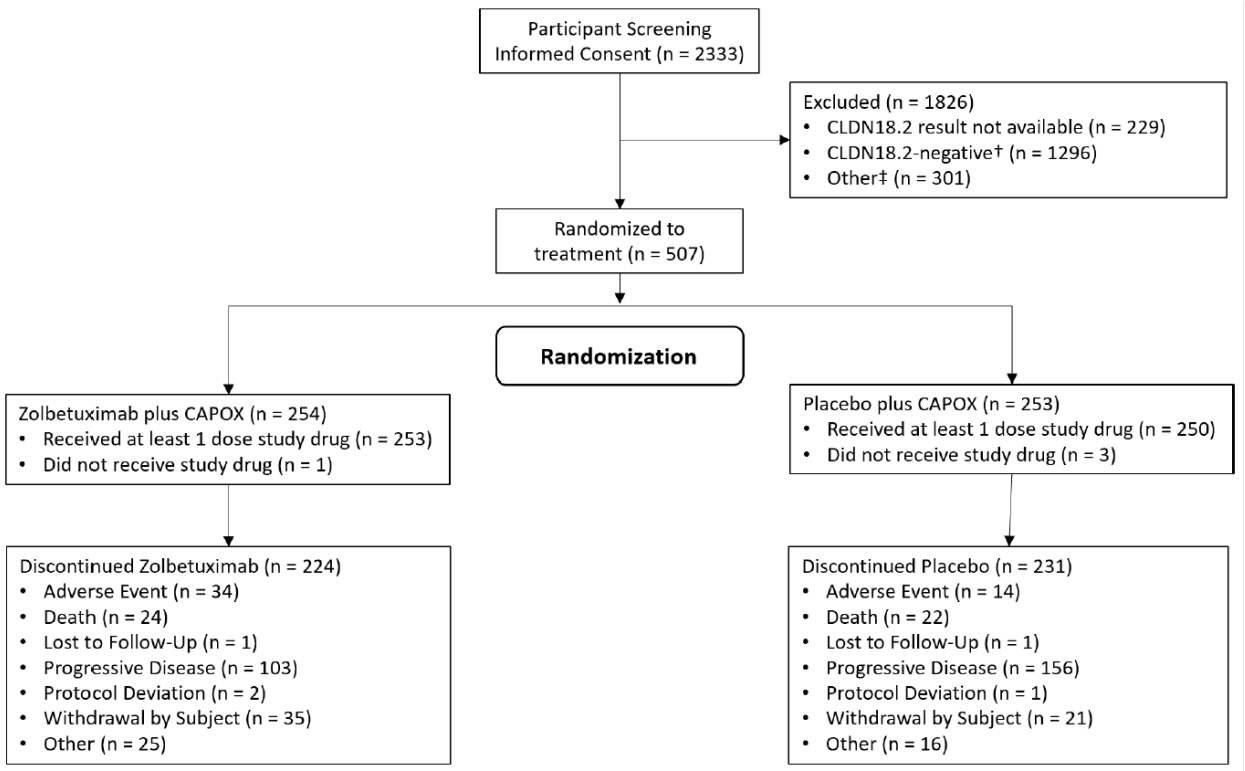
Statistical methods

Statistical methods were defined exactly as in the SPOTLIGHT study, see above.

Results

Participant flow

Figure 12: Participant disposition



CLDN18.2 not available was defined as participants for whom valid IHC results were not obtained.

‡ "Other" represents participants whose tumours were CLDN18.2-positive but failed screening for other reasons including withdrawal by participant, laboratory findings, HER2-expression status, and Eastern Cooperative Oncology Group performance-status score.

Table 48: End of Treatment – Zolbetuximab/Placebo (SAF)

Parameter Category	Arm A Zolbetuximab + CAPOX (n = 254) n %	Arm B Placebo + CAPOX (n = 249) n %	Overall (n = 503) n %
Zolbetuximab/Placebo Discontinuation			
No	30 (11.8)	18 (7.2)	48 (9.5)
Yes	224 (88.2)	231 (92.8)	455 (90.5)
Primary Study Drug Treatment Status			
Adverse Event	34 (13.4)	14 (5.6)	48 (9.5)
Death	24 (9.4)	22 (8.8)	46 (9.1)
Lost to Follow-Up	1 (0.4)	1 (0.4)	2 (0.4)
Progressive Disease	103 (40.6)	156 (62.7)	259 (51.5)
Protocol Deviation	2 (0.8)	1 (0.4)	3 (0.6)
Withdrawal by Subject	35 (13.8)	21 (8.4)	56 (11.1)
Pregnancy	0	0	0
Other	25 (9.8)	16 (6.4)	41 (8.2)
If Progressive Disease or Death †			
Radiographic Progression	85 (33.5)	138 (55.4)	223 (44.3)
Clinical Progression	38 (15.0)	62 (24.9)	100 (19.9)

† Some participants had both radiographic and clinical progression.

Table 49: End of Treatment – CAPOX (SAF)

Parameter	Category	Arm A (N=254)	Arm B (N=249)	Overall (N=503)
CAPOX Discontinuation	No [1]	35 (13.8%)	32 (12.9%)	67 (13.3%)
	Yes	219 (86.2%)	217 (87.1%)	436 (86.7%)
Primary Study Drug Treatment Status	Completed	14 (5.5%)	20 (8.0%)	34 (6.8%)
	Adverse Event	43 (16.9%)	28 (11.2%)	71 (14.1%)
	Death	18 (7.1%)	19 (7.6%)	37 (7.4%)
	Lost to Follow-Up	1 (0.4%)	1 (0.4%)	2 (0.4%)
	Progressive Disease	89 (35.0%)	131 (52.6%)	220 (43.7%)
	Protocol Deviation	2 (0.8%)	0	2 (0.4%)
	Withdrawal by Subject	34 (13.4%)	16 (6.4%)	50 (9.9%)
	Pregnancy	0	0	0
	Other	32 (12.6%)	22 (8.8%)	54 (10.7%)

Recruitment

Date of First Participant Screened: 28 Nov 2018

Data Cutoff Date for Present Primary Analysis: 07 Oct 2022

The median follow-up time for the PFS analysis was 12.62 months (95% CI 10.32, 15.21) in the zolbetuximab plus CAPOX arm and 12.09 months (95% CI 10.25, 15.05) in the placebo plus CAPOX arm. The median follow-up time for the OS analysis was 17.71 months (95% CI 16.33, 19.91) and 18.43 months (95% CI 17.48, 20.80), respectively.

The study was conducted in 18 countries with 166 sites screening at least one participant. Number of patients enrolled across countries:

Asia: China (145), Japan (51), South Korea (50), Thailand (39), Malaysia (19), Taiwan (11);

Europe: Spain (57), Turkey (37), Portugal (26), Romania (25), Greece (12), United Kingdom (10), Croatia (6), Netherlands (6), Ireland (3);

North America: United States (6), Canada (2); South America: Argentina (2);

Conduct of the study

Protocol amendments

Original protocol Version 1.0 (26 Apr 2018) - Protocol amendments introduced for study GLOW are the same as for study SPOTLIGHT (with the exception of a different date of protocol Version 2.0 (29 Jun 2018 for GLOW).

Changes in planned analyses, please see study SPOTLIGHT.

COVID-19 Impact Summary, same as for study SPOTLIGHT, please see clinical AR for details of Urgent Safety Measures implemented for three sites in Spain and Portugal).

Protocol deviations

Table 50: Major Protocol Deviations (SAF)

Deviation Code	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 249)	Overall (n = 503)
Any Deviation, n (%) †	62 (24.4)	46 (18.5)	108 (21.5)
PD1	22 (8.7)	18 (7.2)	40 (8.0)
PD2	5 (2.0)	6 (2.4)	11 (2.2)
PD3	35 (13.8)	25 (10.0)	60 (11.9)
PD4	2 (0.8)	1 (0.4)	3 (0.6)

PD: Protocol deviation
PD1: Entered into the study even though they did not satisfy entry criteria.
PD2: Developed withdrawal criteria during the study and was not withdrawn.
PD3: Received wrong treatment or incorrect dose.
PD4: Received excluded concomitant treatment

The most frequently reported major protocol deviations (11.9%) were for participants who received the wrong treatment or an incorrect dose (category 3); this was mainly due to incorrect capecitabine dosing (approximately 41% of all recorded PD3), the use of incorrect infusion material for zolbetuximab/placebo administration, particularly related to the omission of an add-in infusion filter with the infusion line (approximately 20% of all recorded PD3) and participants receiving CAPOX at an incorrect dosing interval (approximately 16% of all recorded PD3). The next most frequently reported major protocol deviations (8%) were for participants who were enrolled without meeting all of the study entry criteria (with not meeting required laboratory results in approximately 33% of all recorded PD1, not signing the most recent informed consent form and violation of required QTc interval, each in 20% of all recorded PD1). As claimed by the Applicant, the majority of violations were corrected prior to C1D1 dosing (by submission of [repeated] safety labs, signing of correct Informed Consent Form and confirmation of eligible QTc interval at repeated ECG).

For incidences of accident unblinding, please see section 2.6.5 above.

Baseline data

Table 51: Demographic Characteristics (FAS)

Parameter Category	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)	Overall (n = 507)
Sex, n (%)			
Male	159 (62.6)	156 (61.7)	315 (62.1)
Female	95 (37.4)	97 (38.3)	192 (37.9)
Ethnicity, n (%)			
Hispanic or Latino	10 (4.0)	7 (2.8)	17 (3.4)
Not Hispanic or Latino	242 (96.0)	241 (97.2)	483 (96.6)
Missing	2	5	7
Race, n (%)			
White	94 (37.3)	90 (36.3)	184 (36.8)
Black or African American	0	0	0
Asian	158 (62.7)	158 (63.7)	316 (63.2)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Missing	2	5	7
Age (Years)			
N	254	253	507
Mean (SD)	58.6 (12.1)	56.7 (13.0)	57.6 (12.6)
Median (min, max)	61.0 (22, 82)	59.0 (21, 83)	60.0 (21, 83)
Age Group 1 (Years), n (%)			
≤65	176 (69.3)	180 (71.1)	356 (70.2)
>65	78 (30.7)	73 (28.9)	151 (29.8)
Age Group 2 (Years), n (%)			
≤75	242 (95.3)	239 (94.5)	481 (94.9)
>75	12 (4.7)	14 (5.5)	26 (5.1)
ECOG Status at Baseline, n (%)			
0	108 (42.7)	108 (43.2)	216 (42.9)
1	145 (57.3)	142 (56.8)	287 (57.1)
Missing	1	3	4
Weight (kg)			
N	253	250	503
Mean (SD)	61.60 (13.60)	60.17 (12.73)	60.89 (13.18)
Median (min, max)	60.50 (35.5, 111.2)	59.55 (29.1, 100.0)	60.00 (29.1, 111.2)
Height (cm)			
N	253	250	503
Mean (SD)	164.66 (8.68)	165.11 (8.52)	164.88 (8.59)
Median (min, max)	165.00 (145.0, 189.0	165.00 (141.5, 189.0	165.00 (141.5, 189.0)
BMI (kg/m^2)			
N	253	250	503
Mean (SD)	22.79 (4.32)	22.05 (3.79)	22.42 (4.08)
Median (min, max)	22.12 (14.9, 44.3)	21.77 (13.1, 34.0)	21.91 (13.1, 44.3)
BSA (m^2)			
N	253	250	503
Mean (SD)	1.67 (0.20)	1.65 (0.20)	1.66 (0.20)
Median (min, max)	1.67 (1.2, 2.3)	1.63 (1.1, 2.3)	1.65 (1.1, 2.3)
Tobacco History, n (%)			
Never	128 (51.2)	132 (53.0)	260 (52.1)
Current	32 (12.8)	33 (13.3)	65 (13.0)
Former	90 (36.0)	84 (33.7)	174 (34.9)
Missing	4	4	8

Table 52: Primary Diagnosis and Baseline Disease Characteristics (FAS)

Parameter Category/statistic	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)	Overall (n = 507)
Primary Diagnosis, n (%)			
Gastric adenocarcinoma	219 (86.2)	209 (82.6)	428 (84.4)
GEJ adenocarcinoma	35 (13.8)	44 (17.4)	79 (15.6)
Duration Since Initial Diagnosis (days)			
N	242	246	488
Mean (SD)	230.2 (462.0)	243.0 (609.5)	236.6 (540.9)
Median (Min, Max)	44.0 (12, 2396)	43.5 (2, 6010)	44.0 (2, 6010)
Tumor Location, n (%)			
Gastric			
N	219	209	428
Proximal	73 (33.3)	73 (34.9)	146 (34.1)
Distal	90 (41.1)	83 (39.7)	173 (40.4)
Unknown	56 (25.6)	53 (25.4)	109 (25.5)
GEJ			
N	35	44	79
Proximal	15 (42.9)	21 (47.7)	36 (45.6)
Distal	10 (28.6)	13 (29.5)	23 (29.1)
Unknown	10 (28.6)	10 (22.7)	20 (25.3)
Tumor Type, n (%)			
Diffuse	87 (34.4)	100 (39.5)	187 (37.0)
Intestinal	36 (14.2)	41 (16.2)	77 (15.2)
Mixed	20 (7.9)	21 (8.3)	41 (8.1)
Unknown	76 (30.0)	64 (25.3)	140 (27.7)
Other	34 (13.4)	27 (10.7)	61 (12.1)
Missing	1	0	1
Primary Tumor (T), n (%)			
TX	65 (25.6)	47 (18.6)	112 (22.1)
T0	1 (0.4)	0	1 (0.2)
Tis	0	0	0
T1	1 (0.4)	1 (0.4)	2 (0.4)
T1a	0	2 (0.8)	2 (0.4)
T1b	1 (0.4)	2 (0.8)	3 (0.6)
T2	20 (7.9)	12 (4.7)	32 (6.3)
T3	63 (24.8)	63 (24.9)	126 (24.9)
T4	36 (14.2)	44 (17.4)	80 (15.8)
T4a	47 (18.5)	62 (24.5)	109 (21.5)
T4b	20 (7.9)	20 (7.9)	40 (7.9)

Parameter Category/statistic	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)	Overall (n = 507)
Regional Lymph Nodes (N), n (%)			
NX	82 (32.3)	64 (25.3)	146 (28.8)
N0	23 (9.1)	25 (9.9)	48 (9.5)
N1	48 (18.9)	39 (15.4)	87 (17.2)
N2	45 (17.7)	51 (20.2)	96 (18.9)
N3	31 (12.2)	47 (18.6)	78 (15.4)
N3a	15 (5.9)	14 (5.5)	29 (5.7)
N3b	10 (3.9)	13 (5.1)	23 (4.5)
Distant Metastasis (M), n (%) †			
M0	59 (23.3)	56 (22.1)	115 (22.7)
M1	194 (76.7)	197 (77.9)	391 (77.3)
Missing	1	0	1
Tumor Metastatic, n (%) †			
No	32 (12.6)	31 (12.3)	63 (12.4)
Yes	222 (87.4)	222 (87.7)	444 (87.6)
Metastasis Location (≥5% participants in any treatment group), n (%) ‡			
Abdominal cavity	16 (6.3)	9 (3.6)	25 (4.9)
Bone	18 (7.1)	26 (10.3)	44 (8.7)
Liver	73 (28.7)	57 (22.5)	130 (25.6)
Lung	18 (7.1)	21 (8.3)	39 (7.7)
Lymph node	131 (51.6)	119 (47.0)	250 (49.3)
Ovary	21 (8.3)	21 (8.3)	42 (8.3)
Peritoneum	83 (32.7)	91 (36.0)	174 (34.3)
History of *H. Pylori* Infection, n (%)			
No	102 (40.2)	114 (45.1)	216 (42.6)
Yes	44 (17.3)	35 (13.8)	79 (15.6)
Unknown	108 (42.5)	104 (41.1)	212 (41.8)
Barrett's Esophagus Diagnosed, n (%)			
No	150 (59.1)	163 (64.4)	313 (61.7)
Yes	4 (1.6)	3 (1.2)	7 (1.4)
Unknown	100 (39.4)	87 (34.4)	187 (36.9)
CLDN18.2 Testing Result, n (%)			
<75%	0 §	0	0
≥75%	254 (100.0)	253 (100.0)	507 (100.0)
HER2-positive Status, n (%)	0	0	0
Measurable Disease Based on Central Imaging (Yes), n (%)	195 (76.8)	205 (81.0)	400 (78.9)
Measurable Disease Based on Local Imaging (Yes), n (%)	206 (81.1)	209 (82.6)	415 (81.9)

† Distant metastases (M1) and tumor metastatic (Y) may differ depending on date of initial diagnosis ("distant metastasis" refers to disease status at initial diagnosis; "tumor metastatic" refers to status at study entry).

‡ Other metastasis locations and the percentage of participants reporting them overall were adrenal gland (4.3%), omentum (3.9%), pleura (2.4%), colon (2.2%), pelvis (1.8%), stomach (1.8%), mediastinum (1.2%), retroperitoneum (1.2%), pancreas (1.0%), small intestine (0.8%), spleen (0.8%), pericardium (0.6%), bladder (0.4%), rectum (0.4%), bile duct (0.2%), esophagus (0.2%), kidney (0.2%), neck (0.2%), skin (0.2%), testis (0.2%) and/or other (5.9%).

§ CLDN18.2 testing result is based on testing results generated during screening and prior to randomization.

One subject was randomized based on a positive CLDN18.2 status but was later rescored after randomization (in response to a diagnostic protocol deviation) as CLDN18.2 negative.

Table 53: Stratification factors reported at randomization by IRT (FAS)

Parameter, n (%)	Arm A (N=254)	Arm B (N=253)	Overall (N=507)
Region=Asia	157 (61.8%)	158 (62.5%)	315 (62.1%)
Region=Non-Asia	97 (38.2%)	95 (37.5%)	192 (37.9%)
Number of Metastatic Sites=0-2	189 (74.4%)	188 (74.3%)	377 (74.4%)
Number of Metastatic Sites=>=3	65 (25.6%)	65 (25.7%)	130 (25.6%)
Prior Gastrectomy=Yes	75 (29.5%)	75 (29.6%)	150 (29.6%)
Prior Gastrectomy=No	179 (70.5%)	178 (70.4%)	357 (70.4%)

Prior and concomitant medication

The frequency of prior and concomitant medication use was overall similar across the treatment groups; however, higher use of concomitant medications in the zolbetuximab arm vs the placebo arm was reported for e.g., antiemetics (82% and 74%, antihistamines (34% vs 23%), corticosteroids (39% vs 28%), H2-receptor antagonists (18% vs 12%) and colony stimulating factors (23% vs 15%).

Prior anticancer therapy

Overall, 18.3% participants had received prior chemotherapy in the neoadjuvant/adjuvant setting (19.7% in the zolbetuximab arm and 17% in the placebo arm). Prior radiation therapy was received by 3.9% participants (3.5% and 4.3% in both arms). Reasons for radiation were primary disease (1%), palliation (1.8%) and other (1.6%).

Subsequent anticancer therapies

Table 54: New anticancer therapies (FAS) (most common, excerpt from CSR Table 9.2.2.6.1)

Therapeutic group; n (%) **Chemical group (most common)**	**Arm A** **Zolbetuximab + CAPOX** **(N=254)**	**Arm B** **Placebo + CAPOX** **(N=253)**	**Overall** **(N=507)**
Overall	118 (46.5%)	140 (55.3%)	258 (50.9%)
Antineoplastic agents	115 (45.3%)	135 (53.4%)	250 (49.3%)
Taxanes Paclitaxel	69 (27.2%) 46 (18.1%)	79 (31.2%) 51 (20.2%)	148 (29.2%) 97 (19.1%)
Pyrimidine analagoues	33 (13.0%)	44 (17.4%)	77 (15.2%)
(TOP1 inhibitors) Irinotecan	20 (7.9%)	24 (9.5%)	44 (8.7%)
Platinum compounds	27 (10.6%)	19 (7.5%)	46 (9.1%)
VEGF/VEGFR inhibitors Ramucirumab	21 (8.3%)	28 (11.1%)	49 (9.7%)
VEGFR TKI	9 (3.5%)	7 (2.8%)	16 (3.2%)
PD-1/PDL-1 inhibitors	32 (12.6%)	34 (13.4%)	66 (13.0%)
Nivolumab	17 (6.7%)	12 (4.7%)	29 (5.7%)
Sintilimab	6 (2.4%)	11 (4.3%)	17 (3.4%)
Pembrolizumab	5 (2.0%)	4 (1.6%)	9 (1.8%)
Combination of antineoplastic agents	21 (8.3%)	22 (8.7%)	43 (8.5%)

Numbers analysed

Table 55: Analysis Sets (All Randomized Participants)

Analysis Set	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)	Overall (n = 507)
Randomized	254 (100.0)	253 (100.0)	507 (100.0)
Participants who took study drug †	253 (99.6)	250 (98.8)	503 (99.2)
Participants who did not take study drug	1 (0.4)	3 (1.2)	4 (0.8)
Safety analysis set (SAF) ‡	254 (100.0)	249 (98.4) ††	503 (99.2)
Full analysis set (FAS) §	254 (100.0)	253 (100.0)	507 (100.0)
Pharmacokinetics analysis set ¶	245 (96.5)	0	245 (48.3)

† Participants are counted under the randomized arms.
‡ All participants who received at least 1 dose of any study drug (zolbetuximab/placebo/CAPOX). If a participant received at least 1 dose of zolbetuximab, the subject is counted under Arm A.
§ All participants who were randomized to 1 of the treatment arms.
¶ All participants from the SAF for which at least 1 zolbetuximab concentration measurement was available.
† † One participant in Arm B received zolbetuximab and was counted in Arm A.

Outcomes and estimation – GLOW

Primary endpoint - **PFS** assessed by IRC

The primary PFS analysis was conducted with 309 PFS events (planned with 300 events) at the data cutoff date of 07 Oct 2022. Results are statistically significant.

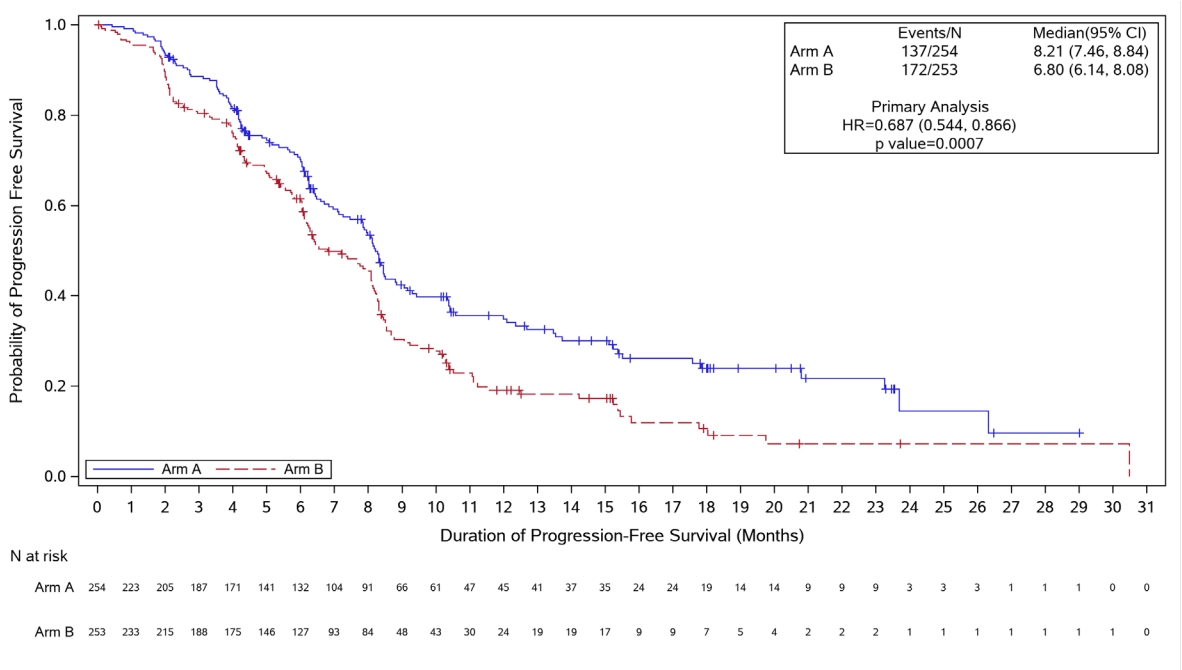
Table 56: PFS Assessed by IRC per RECIST v1.1 – FAS (GLOW)

Parameter	Arm A Zolbetuximab plus CAPOX (n = 254)	Arm B Placebo plus CAPOX (n = 253)
PFS events, n (%)	137 (53.9)	172 (68.0)
Radiographical progression	77 (30.3)	103 (40.7)
Death without documented progression	60 (23.6)	69 (27.3)
Censored, n (%)	117 (46.1)	81 (32.0)
Duration of PFS (months)†		
Median (95% CI)	**8.21** (7.46, 8.84)	**6.80** (6.14, 8.08)
1st Quartile (95% CI)	4.86 (4.17, 6.05)	4.07 (2.96, 4.37)
3rd Quartile (95% CI)	17.84 (13.47, 26.32)	10.38 (8.67, 12.48)
Range‡	0.03+, 29.01+	0.03+, 30.49
Stratified Analysis§		
1-sided P value¶	0.0007	
Hazard ratio (95% CI)††	**0.687 (0.544, 0.866)**	
Median follow-up time (months)‡‡	12.62 (10.32, 15.21)	12.09 (10.25, 15.05)
PFS Rate, % (95% CI)§§		
At 6 months	70.20 (63.42, 75.96)	61.47 (54.82, 67.45)
At 12 months	34.86 (27.75, 42.05)	19.13 (13.50, 25.51)
At 18 months	23.91 (17.09, 31.38)	10.62 (5.68, 17.33)
At 24 months	14.49 (6.17, 26.19)	7.28 (2.99, 14.16)
At 30 months	NE (NE, NE)	7.28 (2.99, 14.16)

Data cutoff: 07 Oct 2022.
CAPOX: capecitabine and oxaliplatin; CI: confidence interval; FAS: full analysis set; IRC: independent review committee; NE: not estimable; PFS: progression-free survival
† Based on Kaplan-Meier estimate.
‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology.
¶ Based on 1-sided log-rank test.
†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

‡‡ Based on reverse Kaplan-Meier estimate.
§§ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Figure 13: Kaplan-Meier Plot of PFS Assessed by IRC – FAS (GLOW)



Data cutoff: 07 Oct 2022.

Updated PFS results

Table 57: Updated PFS by IRC per RECIST v1.1 (at the time of final OS analysis, DCO 25 Mar 2024)

Measure	GLOW	
	Arm A (N=254)	**Arm B (N=253)**
PFS Events, n (%)	153 (60.2)	182 (71.9)
Radiographical Progression	85 (33.5)	108 (42.7)
Death without Documented Progression	68 (26.8)	74 (29.2)
Censored, n (%)	101 (39.8)	71 (28.1)
Duration of PFS (Months) [1]		
Median (95% CI)	**8.21** (7.26, 8.84)	**6.80** (6.14, 8.08)
Stratified Analysis [2]		
1-sided P-value [3]	0.0005	
HR (95% CI) [4]	**0.689 (0.552, 0.860)**	
Median Follow-Up Time, Months (95% CI) [5]	20.57 (15.21, 23.62)	23.49 (10.38, 25.76)
PFS Rate, % (95% CI) [6]		
At 6 months	69.72 (62.92, 75.51)	61.30 (54.63, 67.30)
At 12 months	34.05 (27.14, 41.06)	19.49 (13.96, 25.71)
At 18 months	23.25 (17.09, 29.98)	12.05 (7.50, 17.75)
At 24 months	16.19 (10.63, 22.80)	7.25 (3.69, 12.40)
At 30 months	12.79 (7.60, 19.38)	6.04 (2.73, 11.22)
At 36 months	11.63 (6.62, 18.17)	4.53 (1.60, 9.89)

[1] Based on Kaplan-Meier (KM) estimate.

[2] Stratification factors are Region, Number of Metastatic Sites and Prior Gastrectomy from interactive response technology (IRT).

[3] Based on 1-sided log-rank test.

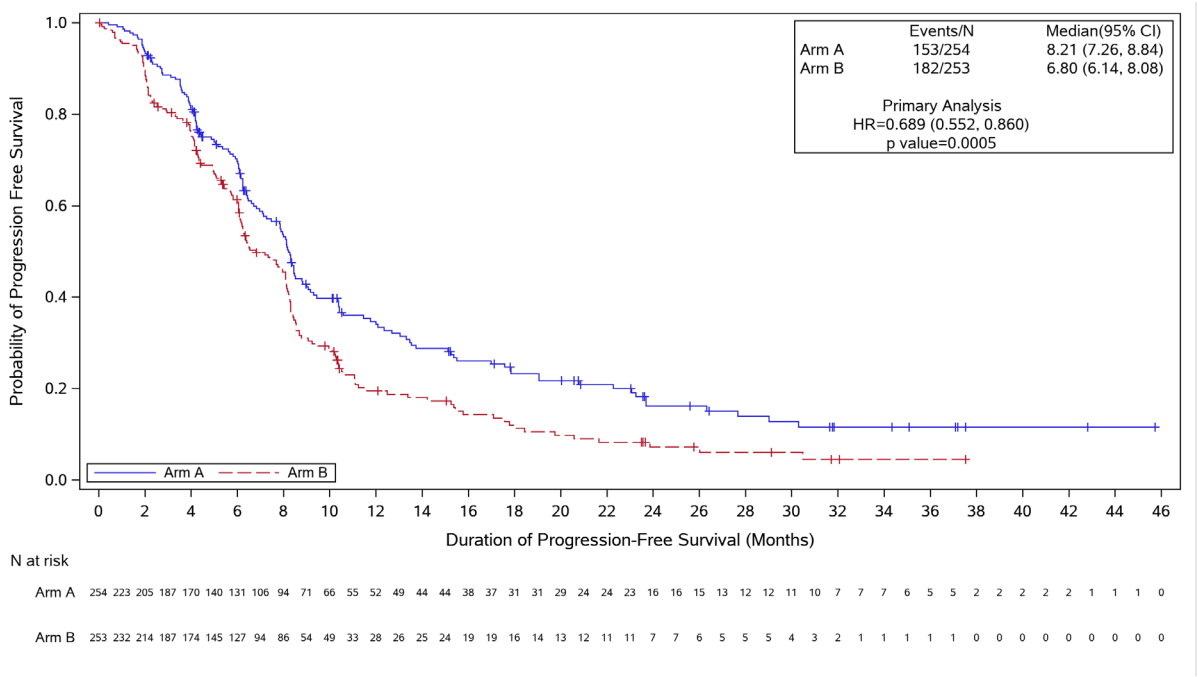
[4] Based on Cox proportional hazards model with treatment as the only explanatory variable. Assuming proportional hazards, an HR < 1 indicates a reduction in hazard rate in favor of treatment arm.

[5] Based on reverse KM estimate.

[6] PFS rate and 95% CI are estimated using KM method and Greenwood formula.

Arm A = Zolbetuximab + CAPOX, Arm B = Placebo + CAPOX.

Figure 14: Kaplan-Meier Plot of PFS by IRC - FAS (GLOW); DCO 25 Mar 2024



For subgroup analyses, please see Ancillary analyses.

Secondary endpoints

OS

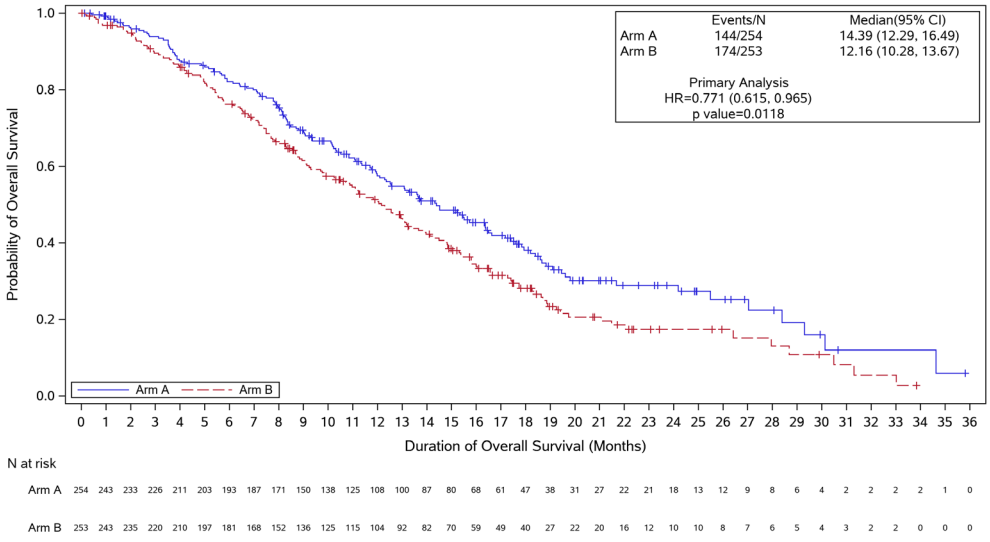
Table 58: Overall Survival – FAS (GLOW) – interim analysis (DCO 07 Oct 2022)

Parameter	Arm A Zolbetuximab plus CAPOX (n = 254)	Arm B Placebo plus CAPOX (n = 253)
Deaths, n (%)	144 (56.7)	174 (68.8)
Censored, n (%)	110 (43.3)	79 (31.2)
Censored at cutoff date, n (%)	16 (6.3)	11 (4.3)
Duration of Overall Survival (months)†		
Median (95% CI)	**14.39** (12.29, 16.49)	**12.16** (10.28, 13.67)
1st Quartile (95% CI)	8.05 (6.70, 8.80)	6.51 (5.19, 7.49)
3rd Quartile (95% CI)	27.04 (19.45, 30.13)	18.69 (17.28, 22.05)
Range‡	0.03+, 35.81+	0.03+, 33.84+
Stratified Analysis§		
1-sided P value¶	0.0118	
Hazard ratio (95% CI)††	**0.771 (0.615, 0.965)**	
Median follow-up time (months)‡‡	17.71 (16.33, 19.91)	18.43 (17.48, 20.80)
Overall Survival Rate, % (95% CI)§§		
At 12 months	57.54 (50.71, 63.77)	50.79 (44.12, 57.06)
At 18 months	38.10 (30.96, 45.19)	28.14 (21.95, 34.65)
At 24 months	28.92 (21.75, 36.46)	17.38 (11.62, 24.12)
At 30 months	16.01 (7.73, 26.95)	10.87 (5.12, 19.06)
At 36 months	NE (NE, NE)	NE (NE, NE)

Data cutoff: 07 Oct 2022.
† Based on Kaplan-Meier estimate. ‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the IRT.
¶ Based on 1-sided log-rank test.
†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. ‡‡ Based on reverse Kaplan-Meier estimate.
§§ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Results of the analysis met statistical significance.

Figure 15: Kaplan-Meier Plot of Overall Survival – FAS (GLOW) (data cut off 07 Oct 2022)



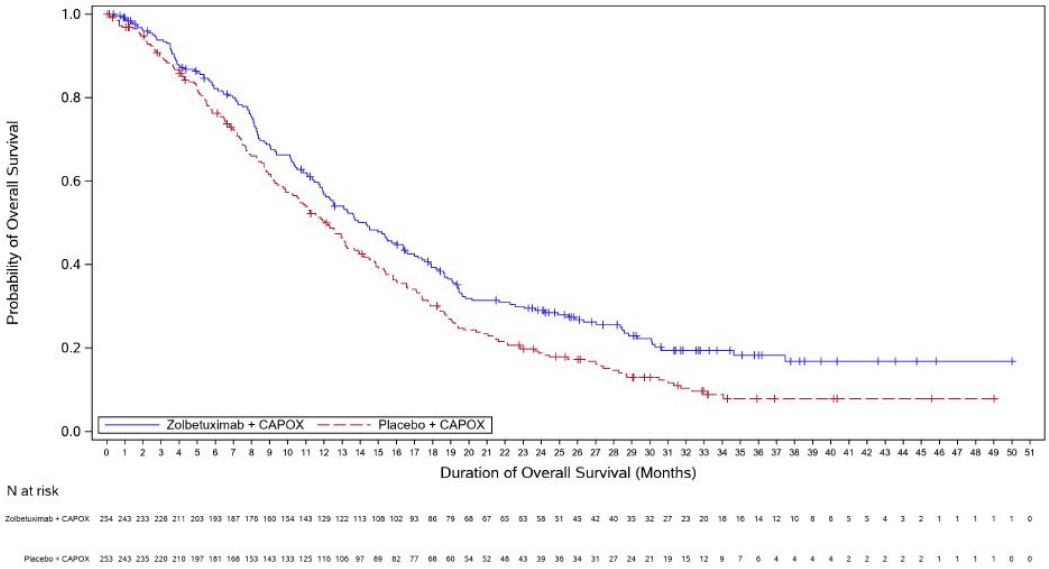
Updated OS results

Table 59*:* OS GLOW (final OS analyses)

Parameter	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)
Deaths, n (%)	180 (70.9)	207 (81.8)
Censored, n (%)	74 (29.1)	46 (18.2)
Censored at cutoff date, n (%)	9 (3.5)	2 (0.8)
Duration of Overall Survival, Months†		
Median (95% CI)	**14.32** (12.09, 16.39)	**12.16** (10.28, 13.67)
1st quartile (95% CI)	8.05 (6.70, 8.71)	6.51 (5.19, 7.49)
3rd quartile (95% CI)	28.39 (22.28, 34.63)	19.42 (17.74, 23.66)
Range‡	0.03+, 50.00+	0.03+, 49.02+
Stratified Analysis§		
1-sided P-value ¶	0.0047	
HR (95% CI)††	**0.763** (0.622, 0.936)	
Median Follow-Up Time, Months (95% CI)§§	31.70 (28.19, 33.71)	32.95 (29.70, 35.91)
Overall Survival Rate, % (95% CI)¶¶		
At 12 months	56.68 (50.08, 62.75)	50.44 (43.89, 56.61)
At 18 months	39.32 (32.98, 45.58)	30.14 (24.34, 36.13)
At 24 months	29.02 (23.21, 35.06)	18.81 (14.01, 24.16)
At 30 months	22.25 (16.75, 28.24)	13.00 (8.88, 17.92)
At 36 months	18.30 (12.95, 24.39)	7.88 (4.41, 12.63)
At 42 months	16.77 (11.28, 23.20)	7.88 (4.41, 12.63)
At 48 months	16.77 (11.28, 23.20)	7.88 (4.41, 12.63)
At 54 months	NE (NE, NE)	NE (NE, NE)

Data cutoff: 12 Jan 2024
CAPOX: capecitabine and oxaliplatin; CI: confidence interval; eCRF: electronic case report form; FAS: full analysis set; HR: hazard ratio; NE: non-estimable
† Based on Kaplan-Meier estimate
‡ + indicates censoring
§ Stratification factors were region, number of metastatic sites and prior gastrectomy from interactive response technology.
¶ Based on 1-sided log-rank test
†† Based on Cox proportional hazards model with treatment as the only explanatory variable. Assuming proportional hazards, an HR < 1 indicates a reduction in the hazard rate in favor of the treatment arm.
§§ Based on reverse Kaplan-Meier estimate
¶¶ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Figure 16: KM Plot of updated Overall Survival – FAS (GLOW) (data cut off 12-Jan-2024)



For subgroup analyses, please see Ancillary analyses

TTCD - time to first confirmed deterioration

Table 60: TTCD for Physical Functioning, OG25-Pain and GHS/QoL (Primary Thresholds, Excluding Death) – FAS (GLOW) (excerpt)

Parameter	Arm A Zolbetuximab plus CAPOX (n = 254)	Arm B Placebo plus CAPOX (n = 253)
Physical Functioning (Deterioration Threshold = 13†)		
Total number of participants, n (%)	254 (100.0)	253 (100.0)
Deterioration events, n (%)	99 (39.0)	109 (43.1)
Censored, n (%)	155 (61.0)	144 (56.9)
Time to First Confirmed Physical Functioning Deterioration (months)‡		
Median (95% CI)	**8.31** (5.88, 19.81)	**7.92** (6.47, 11.10)
Stratified analysis§		
1-sided P value¶	0.4980	
Hazard ratio (95% CI)††	**0.999 (0.759, 1.315)**	
OG25-Pain (Deterioration Threshold = 16.7†)		
Total number of participants, n (%)	254 (100.0)	253 (100.0)
Deterioration events, n (%)	44 (17.3)	40 (15.8)
Censored, n (%)	210 (82.7)	213 (84.2)
Time to First Confirmed OG25-Pain Deterioration (months)‡		
Median (95% CI)	NYR	25.82 (NE, NE)
Stratified analysis§		
1-sided P value¶	0.3880	
Hazard ratio (95% CI)††	**1.066 (0.692, 1.642)**	
GHS/QoL (Deterioration Threshold = 13†)		
Total number of participants, n (%)	254 (100.0)	253 (100.0)
Deterioration events, n (%)	85 (33.5)	111 (43.9)
Censored, n (%)	169 (66.5)	142 (56.1)
Time to First Confirmed GHS/QoL Deterioration (months)‡		
Median (95% CI)	**9.69** (7.39, NE)	**7.49** (6.11, 9.86)
Stratified analysis§		
1-sided P value¶	0.1299	
Hazard ratio (95% CI)††	**0.847 (0.636, 1.129)**	

Data cutoff: 07 Oct 2022. NE: not estimable; NYR: not yet reached;
† The threshold values of 13 for Physical Functioning and GHS/QoL are based on [Cocks et al, 2012] and the threshold value of 16.7 for OG25-Pain is based on [Norman et al, 2003] and [Sloan et al, 2005].
‡ Time to confirmed deterioration = date of first confirmed clinically meaningful deterioration/censored date – randomization date + 1. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. ¶ Based on 1-sided log-rank test. †† Based on stratified Cox proportional hazard model with region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

ORR and DCR

Table 61: ORR and DCR Assessed by IRC – Unconfirmed Responses (FAS) (DCO 12 Jan 2024)

Parameter	Arm A Zolbetuximab plus CAPOX (n = 254)	Arm B Placebo plus CAPOX (n = 253)
Best Overall Response, n (%)†	210 (82.7)	225 (88.9)
CR	11 (4.3)	4 (1.6)
PR	97 (38.2)	95 (37.5)
Stable disease	47 (18.5)	57 (22.5)
Non-CR/non-progressive disease	39 (15.4)	35 (13.8)
Progressive disease	12 (4.7)	28 (11.1)
Not evaluable	1 (0.4)	5 (20)
No disease	3 (1.2)	1 (0.4)
Not available‡	44	28
ORR, n (%)	108 (**42.5**)	99 (**39.1**)
95% CI for ORR (%)§	(36.36, 48.85)	(33.08, 45.44)
Stratified 1-sided P value¶	0.2219	
DCR, n (%)††	194 (**76.4**)	191 (**75.5**)
95% CI for DCR (%)§	(70.67, 81.46)	(69.72, 80.66)
Stratified 1-sided P value¶	0.4200	

CR: complete response; DCR: disease control rate; ORR: objective response rate; PR: partial response;

† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) was believed to be best response, the assessment should have been at least 8 weeks after randomization. For calculation of percentages, the denominator included the total number of participants in each arm.

‡ No post baseline imaging assessment.

§ Using exact method based on binomial distribution (Clopper-Pearson).

¶ Based on 1-sided Cochran-Mantel-Haenszel test. Stratification factors were region, number of metastatic sites and prior gastrectomy.

†† DCR was defined as the proportion of participants who had a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).

DOR

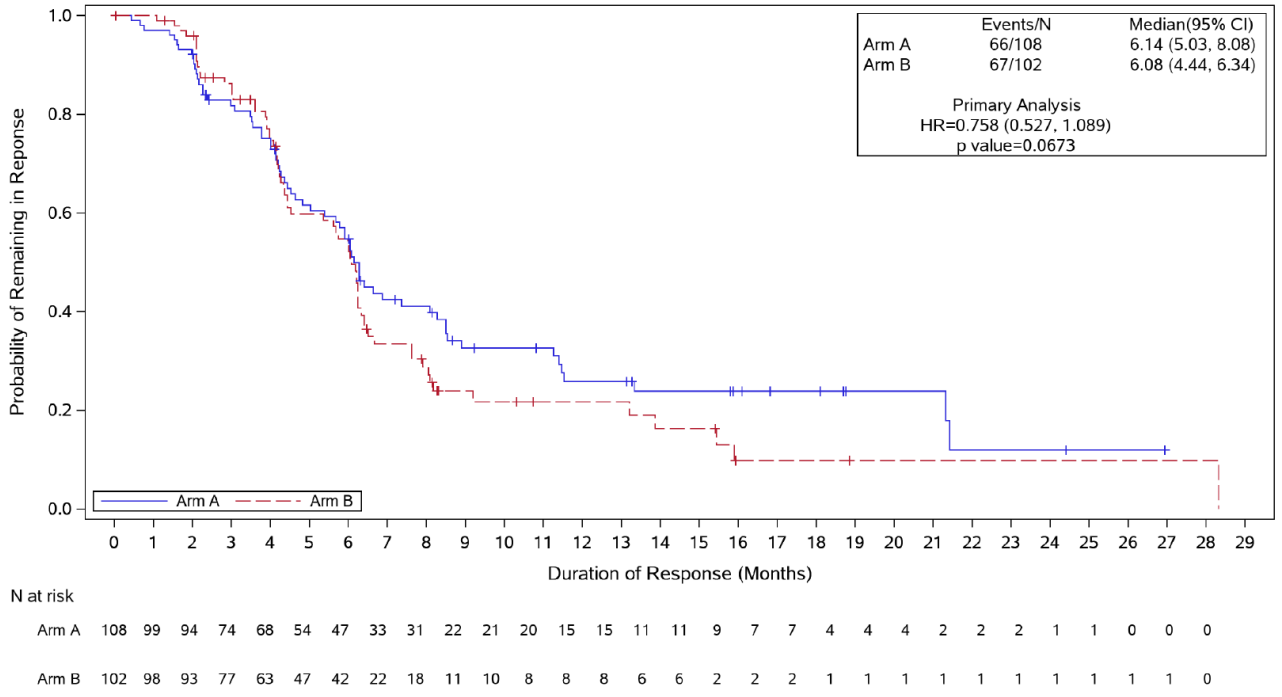
Table 62: Duration of Response Assessed by IRC Unconfirmed Responses – FAS

Parameter	Arm A Zolbetuximab plus CAPOX (n = 108)	Arm B Placebo plus CAPOX (n = 102)
Events, n (%)	66 (61.1)	67 (65.7)
Censored, n (%)	42 (38.9)	35 (34.3)
Duration of Response (months)†		
Median (95% CI)	6.14 (5.03, 8.08)	6.08 (4.44, 6.34)
1st Quartile (95% CI)	4.01 (2.40, 4.37)	3.98 (3.02, 4.34)
3rd Quartile (95% CI)	13.34 (8.54, NE)	8.18 (6.51, 15.44)
Range‡	0.03+, 26.94+	0.03+, 28.32
Stratified Analysis§		
1-sided P value¶	0.0673	
Hazard ratio (95% CI)††	0.758 (0.527, 1.089)	

Data cutoff: 07 Oct 2022. † Based on Kaplan-Meier estimate. ‡ + indicates censoring.

§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test. †† Based on Cox proportional hazard model

Figure 17: KM Plot of DOR, by IRC, unconfirmed responses, FAS



HRQoL

The secondary HRQoL endpoints collected via the EORTC QLQ-C30, QLQ-OG25 plus STO22 Belching subscale, Global Pain (GP) and EQ-5D-5L were analyzed with summary of change from baseline over time through the end of CAPOX treatment and inferential methods.

The compliance rate for completion of the PRO instruments was similar between the treatment arms during the treatment and follow-up periods. Baseline total scores and subscale scores were comparable between the treatment arms. The CIs of the total and subscale mean scores overlapped between the

treatment groups for most visits during the treatment and follow-up periods though no formal statistical testing was performed on these descriptive summary measures.

Exploratory endpoints

Time to progression - TTP

Table 63: Kaplan-Meier Estimate of TTP Assessed by IRC (FAS)

Parameter	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)
Progression Events, n (%)	77 (30.3%)	103 (40.7%)
Radiographical progression, n (%)	77 (30.3%)	103 (40.7%)
Censored, n (%)	177 (69.7%)	150 (59.3%)
TTP, Months †		
Median (95% CI)	11.99 (8.84, 20.80)	8.31 (8.11, 9.95)
1st quartile (95% CI)	6.83 (6.14, 8.18)	6.05 (4.14, 6.18)
3rd quartile (95% CI)	23.69 (23.26, NE)	15.44 (11.07, NE)
Range ‡	0.03+, 29.01+	0.03+, 28.62+
Stratified Analysis §		
1-Sided P value ¶	0.0002	

Deaths were not included as events. For deaths without documented progressive disease (by the IRC), participants were censored at the time of the last evaluable radiological assessment.
† Based on Kaplan-Meier estimate. ‡ + indicates censoring. ¶ Based on 1-sided log-rank test

PFS2

Table 64: Summary of PFS After Subsequent Therapy (PFS2), by Investigator (FAS) (excerpt)

Parameter	Arm A Zolbetuximab + CAPOX (n = 254)	Arm B Placebo + CAPOX (n = 253)
PFS2 Events, n (%)	171 (67.3%)	205 (81.0%)
Progression of disease after new ACT	44 (17.3%)	64 (25.3%)
Death after new ACT	41 (16.1%)	50 (19.8%)
Death from any cause without new ACT	69 (27.2%)	71 (28.1%)
No PD, no death, ended 2nd or started 3rd line ACT	17 (6.7%)	20 (7.9%)
Censored, n (%)	83 (32.7%)	48 (19.0%)
Duration of PFS2, Months †		
Median (95% CI)	11.01 (10.02, 13.11)	9.03 (8.28, 9.89)
Stratified Analysis §		
1-Sided P value ¶	0.0005	
Hazard ratio (95% CI) ††	0.708 (0.575, 0.871)	

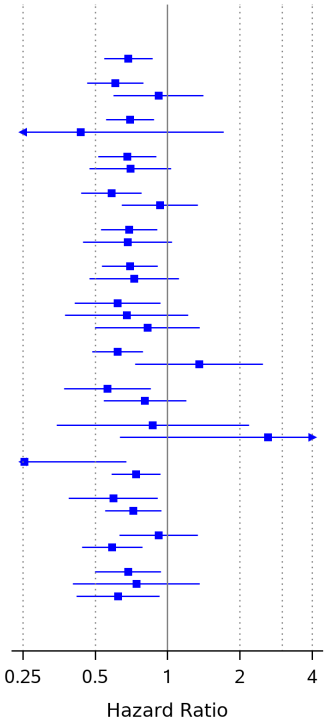
† Based on Kaplan-Meier estimate. ‡ + indicates censoring.
§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from IRT.
¶ Based on 1-sided log-rank test †† Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

Ancillary analyses

Subgroup analyses (based on primary analyses)

Figure 18: Forest Plot for Subgroup Analysis of PFS Assessed by IRC – FAS (GLOW)

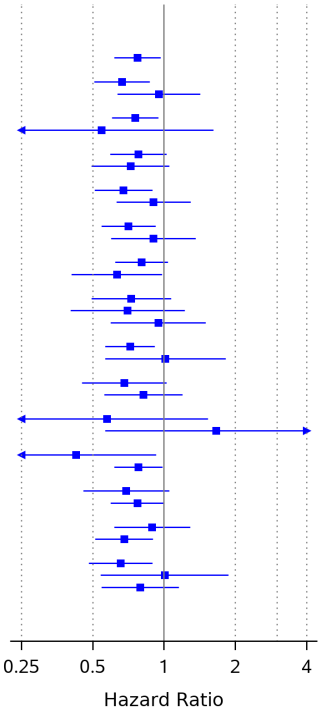
Subgroup	Arm A Event/N	Arm B Event/N	HR [95%CI]
All Subjects	137/254	172/253	0.687 (0.544, 0.866)
Age Group 1: <=65 years	92/176	130/180	0.606 (0.463, 0.794)
>65 years	45/78	42/73	0.917 (0.596, 1.410)
Age Group 2: <=75 years	134/242	165/239	0.698 (0.554, 0.879)
>75 years	3/12	7/14	0.435 (0.111, 1.713)
Sex: Male	92/159	110/156	0.679 (0.513, 0.898)
Female	45/95	62/97	0.700 (0.474, 1.035)
Region: Asia	82/157	109/158	0.583 (0.436, 0.781)
Non-Asia	55/97	63/95	0.928 (0.645, 1.336)
Number of Metastatic Sites: 0-2	97/189	125/188	0.691 (0.529, 0.904)
>=3	40/65	47/65	0.682 (0.445, 1.045)
Prior Gastrectomy: No	97/179	125/178	0.696 (0.533, 0.909)
Yes	40/75	47/75	0.726 (0.472, 1.114)
Tumor Type: Diffuse	38/87	60/100	0.620 (0.411, 0.936)
Intestinal	21/36	26/41	0.675 (0.375, 1.217)
Mixed/Other	28/54	36/48	0.824 (0.499, 1.358)
Medical Condition: Gastric	116/219	149/209	0.619 (0.484, 0.791)
GEJ	21/35	23/44	1.351 (0.731, 2.496)
Gastric Tumor Location: Proximal	40/73	53/73	0.561 (0.370, 0.850)
Distal	46/90	55/83	0.805 (0.542, 1.194)
GEJ Tumor Location: Proximal	9/15	11/21	0.867 (0.345, 2.182)
Distal	4/10	9/13	2.614 (0.632, 10.816)
Country: Japan	7/24	16/27	0.253 (0.095, 0.674)
Non-Japan	130/230	156/226	0.738 (0.584, 0.933)
China	39/76	48/69	0.594 (0.387, 0.910)
Non-China	98/178	124/184	0.719 (0.550, 0.941)
Race: White	52/94	58/90	0.918 (0.629, 1.339)
Asian	83/158	109/158	0.587 (0.440, 0.785)
Tobacco History: Never	73/128	87/132	0.684 (0.499, 0.938)
Current	20/32	24/33	0.742 (0.404, 1.362)
Former	43/90	61/84	0.622 (0.418, 0.927)



Data cutoff: 07 Oct 2022.
In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. The HR reported for all participants was based on stratified analysis.

Figure 19: Forest Plot for Subgroup Analysis of Overall Survival – FAS (GLOW)

Subgroup	Arm A Event/N	Arm B Event/N	HR [95%CI]
All Subjects	144/254	174/253	0.771 (0.615, 0.965)
Age Group 1: <=65 years	92/176	127/180	0.664 (0.507, 0.869)
>65 years	52/78	47/73	0.951 (0.637, 1.420)
Age Group 2: <=75 years	137/242	164/239	0.755 (0.602, 0.948)
>75 years	7/12	10/14	0.544 (0.183, 1.617)
Sex: Male	94/159	114/156	0.779 (0.593, 1.025)
Female	50/95	60/97	0.722 (0.494, 1.054)
Region: Asia	88/157	110/158	0.674 (0.508, 0.893)
Non-Asia	56/97	64/95	0.903 (0.630, 1.294)
Number of Metastatic Sites: 0-2	100/189	126/188	0.708 (0.544, 0.922)
>=3	44/65	48/65	0.903 (0.598, 1.362)
Prior Gastrectomy: No	109/179	125/178	0.804 (0.622, 1.040)
Yes	35/75	49/75	0.632 (0.408, 0.982)
Tumor Type: Diffuse	44/87	63/100	0.726 (0.493, 1.069)
Intestinal	23/36	30/41	0.702 (0.403, 1.222)
Mixed/Other	36/54	37/48	0.945 (0.594, 1.502)
Medical Condition: Gastric	124/219	146/209	0.718 (0.565, 0.913)
GEJ	20/35	28/44	1.013 (0.563, 1.823)
Gastric Tumor Location: Proximal	42/73	51/73	0.680 (0.450, 1.025)
Distal	51/90	56/83	0.819 (0.560, 1.198)
GEJ Tumor Location: Proximal	7/15	13/21	0.575 (0.216, 1.531)
Distal	6/10	8/13	1.663 (0.565, 4.897)
Country: Japan	13/24	19/27	0.425 (0.195, 0.924)
Non-Japan	131/230	155/226	0.779 (0.617, 0.983)
China	40/76	49/69	0.693 (0.456, 1.052)
Non-China	104/178	125/184	0.773 (0.595, 1.004)
Race: White	53/94	60/90	0.891 (0.615, 1.291)
Asian	89/158	110/158	0.678 (0.512, 0.898)
Tobacco History: Never	71/128	93/132	0.656 (0.481, 0.895)
Current	20/32	21/33	1.006 (0.541, 1.873)
Former	52/90	59/84	0.793 (0.545, 1.154)



Data cutoff: 07 Oct 2022.
In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. The HR reported for all participants was based on stratified analysis.

Table 65: Subgroup analysis of ORR, by IRF, unconfirmed responses (GLOW), data cut off 12 Jan 2024

		Arm A			Arm B				
Parameter	Value	N	Events (%)	Median (Months)	N	Events (%)	Median (Months)	Hazard Ratio (HR) 95% CI [1]	P-value [2]
All [3]	-	254	153 (60.2%)	8.21	253	182 (71.9%)	6.80	0.689 (0.552, 0.860)	0.0005
Age Group 1	<=65 years	176	106 (60.2%)	8.31	180	136 (75.6%)	6.44	0.621 (0.480, 0.803)	0.0001
	>65 years	78	47 (60.3%)	7.13	73	46 (63.0%)	8.21	0.984 (0.655, 1.479)	0.4681
Age Group 2	<=75 years	242	149 (61.6%)	8.18	239	175 (73.2%)	6.51	0.703 (0.564, 0.877)	0.0008
	>75 years	12	4 (33.3%)	17.84	14	7 (50.0%)	10.25	0.692 (0.202, 2.373)	0.2812
Sex	Male	159	104 (65.4%)	8.18	156	116 (74.4%)	6.24	0.686 (0.525, 0.896)	0.0027
	Female	95	49 (51.6%)	8.31	97	66 (68.0%)	8.08	0.735 (0.507, 1.067)	0.0519
Region	Asia	157	91 (58.0%)	8.48	158	115 (72.8%)	6.31	0.612 (0.464, 0.809)	0.0003
	Non-Asia	97	62 (63.9%)	7.95	95	67 (70.5%)	8.11	0.900 (0.635, 1.275)	0.2732
Number of Metastatic Sites	0-2	189	111 (58.7%)	8.31	188	134 (71.3%)	7.69	0.707 (0.548, 0.911)	0.0035
	>=3	65	42 (64.6%)	7.89	65	48 (73.8%)	6.05	0.676 (0.444, 1.029)	0.0333
Prior Gastrectomy	No	179	104 (58.1%)	8.21	178	129 (72.5%)	6.54	0.680 (0.524, 0.883)	0.0018
	Yes	75	49 (65.3%)	8.18	75	53 (70.7%)	7.75	0.794 (0.537, 1.173)	0.1220
Tumor Type	Diffuse	87	43 (49.4%)	10.41	100	69 (69.0%)	8.08	0.602 (0.410, 0.883)	0.0044
	Intestinal	36	23 (63.9%)	8.11	41	26 (63.4%)	6.11	0.769 (0.436, 1.357)	0.1829
	Mixed/Other	54	31 (57.4%)	7.46	48	37 (77.1%)	6.37	0.845 (0.523, 1.366)	0.2466
Medical Condition	Gastric	219	131 (59.8%)	8.31	209	158 (75.6%)	6.37	0.640 (0.507, 0.808)	<0.0001
	GEJ	35	22 (62.9%)	6.24	44	24 (54.5%)	9.23	1.275 (0.701, 2.320)	0.2161
Gastric Tumor Location	Proximal	73	43 (58.9%)	10.35	73	56 (76.7%)	6.51	0.576 (0.386, 0.861)	0.0032
	Distal	90	52 (57.8%)	8.11	83	57 (68.7%)	6.28	0.813 (0.557, 1.186)	0.1411
GEJ Tumor Location	Proximal	15	10 (66.7%)	6.24	21	12 (57.1%)	6.24	0.776 (0.315, 1.913)	0.2881
	Distal	10	4 (40.0%)	8.11	13	9 (69.2%)	10.38	2.614 (0.632, 10.816)	0.0850
Country	Japan	24	8 (33.3%)	20.80	27	16 (59.3%)	8.28	0.320 (0.132, 0.779)	0.0044
	Non-Japan	230	145 (63.0%)	8.08	226	166 (73.5%)	6.44	0.750 (0.599, 0.938)	0.0057
	China	76	45 (59.2%)	8.31	69	50 (72.5%)	6.11	0.623 (0.414, 0.936)	0.0112
	Non-China	178	108 (60.7%)	8.18	184	132 (71.7%)	7.75	0.724 (0.559, 0.936)	0.0066
Race	White	94	59 (62.8%)	7.98	90	62 (68.9%)	8.11	0.891 (0.622, 1.276)	0.2617
	Asian	158	92 (58.2%)	8.44	158	115 (72.8%)	6.31	0.616 (0.467, 0.813)	0.0003
Tobacco History	Never	128	80 (62.5%)	8.11	132	92 (69.7%)	6.54	0.732 (0.541, 0.989)	0.0199
	Current	32	20 (62.5%)	8.15	33	25 (75.8%)	7.95	0.753 (0.418, 1.360)	0.1749
	Former	90	51 (56.7%)	8.51	84	64 (76.2%)	6.51	0.589 (0.400, 0.866)	0.0034

Sensitivity analyses

Sensitivity analyses of PFS based on primary PFS analysis

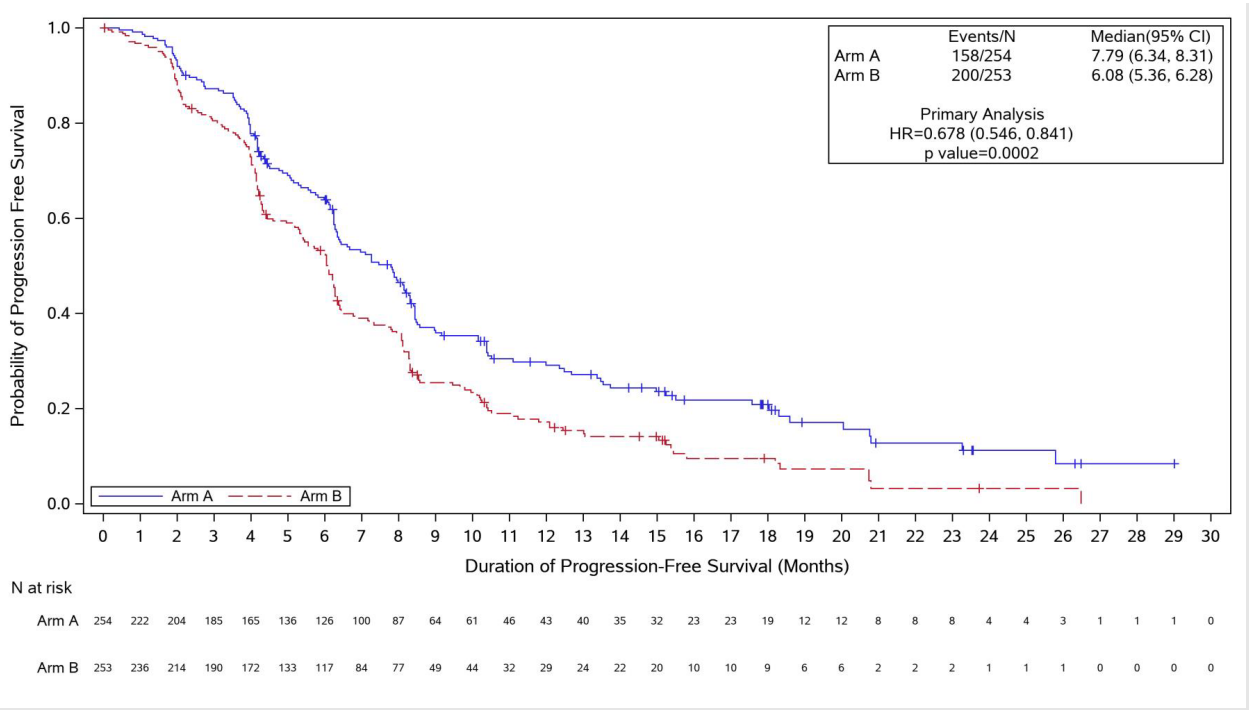
Prespecified sensitivity analysis of PFS were conducted based on investigator assessments, an analysis of the discordance between the IRC and investigator assessments, and a PFS analysis based on informative censoring criteria. For PFS Primary Analysis Definition, please see “statistical methods”.

Table 66*: Sensitivity analyses of PFS, predefined (*assessor´s table from CSR, Tables 13, 14 and 15*)*

Sensitivity analyses of PFS	**HR (95% CI) Nominal P**	**Arm A, Median PFS, Months (95% CI)**	**Arm B, Median PFS, Months (95% CI)**
1) PFS by investigator assessment	0.678 (0.546, 0.841) 0.0002	7.79 (6.34, 8.31)	6.08 (5.36, 6.28)
2) analysis that treats likely informative censoring as PFS events (analysis included various defined events as PFS events rather than censoring [by IRC assessment]): *radiographical progression as assessed by the investigator, clinical progression as assessed by the investigator, worsening of the ECOG performance status, participants receiving a new ACT, participants with clinical progression or worsening of ECOG performance status and missing ≥2 imaging assessments* Note: radiological PD by IRC and death were also included as events	0.714 (0.584, 0.873)	6.51 (6.14, 7.82)	6.05 (5.26, 6.28)
3) censoring of death after new ATC at date of last radiological assessment before start of new ATC (by IRC)	0.689 (0.535, 0.886)	8.31 (7.89, 10.35)	7.95 (6.28, 8.28)
Primary analysis (for comparison)	0.687 (0.544, 0.866) 0.0007	8.21 (7.46, 8.84)	6.80 (6.14, 8.08)

ACT: anticancer therapy

Figure 20: Kaplan-Meier Plot of PFS Assessed by Investigator Assessment – FAS (GLOW)



Data cutoff: 07 Oct 2022

Discordance between IRC and local investigator

Table 67: Discordance between IRC and Local Investigator in PFS Status or Date for Subjects with Measurable Disease (source: CSR Table 9.3.1.2.2)

Variable	Arm A (N=254)	Arm B (N=253)
Overall Disagreement (Either PFS Status or Date), n (%) [1]	73 (28.7%)	109 (43.1%)
Disagreement on PFS Status, n (%)	31 (12.2%)	44 (17.4%)
IRC Event, INV No Event	5 (2.0%)	8 (3.2%)
IRC No Event, INV Event	26 (10.2%)	36 (14.2%)
Disagreement on PFS Event date, n (%) [1]	40 (15.7%)	65 (25.7%)
IRC event date earlier than INV event date	16 (6.3%)	27 (10.7%)
IRC event date later than INV event date	24 (9.4%)	38 (15.0%)
Disagreement on PFS censoring date, n (%) [1]	2 (0.8%)	0
IRC censoring date earlier than INV censoring date	0	0
IRC censoring date later than INV censoring date	2 (0.8%)	0

Sensitivity analyses of ORR

Table 68: Sensitivity analyses for ORR

Sensitivity analysis	**Parameter**	**Arm A Zolbetuximab plus CAPOX (n=254)**	**Arm B Placebo plus CAPOX (n=253)**
ORR by **ICR, confirmed** responses	ORR %	**32.3**	**31.2**
	(95% CI)	(26.6, 38.4)	(25.6, 37.3)
ORR by **investigator, unconfirmed** responses	ORR, n (%)	**40.2**	**38.3**
	(95% CI)	(34.1, 46.5)	(32.3, 44.6)
ORR by **investigator, confirmed** responses	ORR, n (%)	**29.1**	**27.3**
	(95% CI)	(23.6, 35.2)	(21.9, 33.2)
ORR by **ICR, unconfirmed** responses, subjects with **measurable** disease	ORR %	**53.8**	**48.8**
	(95% CI)	(46.6, 60.99)	(41.8, 55.8)

Sensitivity analyses for DOR

Table 69: Sensitivity analyses for DOR

Sensitivity analysis	Parameter	Arm A Zolbetuximab plus mFOLFOX6	Arm B Placebo plus mFOLFOX6
DOR based on **confirmed responses** by **ICR**	**DOR (months)**	N=82	N=79
	Median (95% CI)	8.28 (6.28, 11.40)	6.24 (6.01, 7.62)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.570 (0.363, 0.895)	
DOR based on **investigator** assessment, **confirmed** responses	**DOR (months)**	N=74	N=69
	Median (95% CI)	10.12 (6.37, 14.49)	6.41 (5.78, 8.18)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.616 (0.399, 0.950)	
DOR based on **investigator** assessment, **unconfirmed** responses	**DOR (months)**	N=102	N=97
	Median (95% CI)	6.34 (5.19, 10.12)	5.55 (4.24, 6.24)
	Stratified Analysis		
	Hazard ratio (95% CI)	0.642 (0.453, 0.910)	

2.6.5.4. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 70: Summary of efficacy for trial 8951-CL-0301 (SPOTLIGHT)

Title: A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma			
Study Identifier	ISN/Protocol 8951-CL-0301 EudraCT 2017-002567-17		
Design	Global, multi-center, double-blind, 1:1 randomized, placebo-controlled phase 3 study		
	Duration of Main Phase: Duration of Run-in Phase: Duration of Extension Phase:		From 21 Jun 2018 to 09 Sep 2022 (data cutoff date) Not Applicable Not Applicable
Hypothesis	Superiority		
Treatments Groups	**Arm A**	Zolbetuximab + mFOLFOX6 n = 283	
	Arm B	Placebo + mFOLFOX6 n = 282	
Endpoints and Definitions	Primary Endpoint	PFS	PFS assessed by blinded IRC. Time from date of randomization until the date of radiological disease progression assessed by IRC per RECIST 1.1 or death from any cause, whichever was earliest.
	Key Secondary Endpoint	OS	Time from the date of randomization until the date of death from any cause
	Key Secondary Endpoint	TTCD	Time to first confirmed deterioration, i.e., time from randomization to first clinically meaningful deterioration that was confirmed at the next scheduled visit. TTCD was defined for the following 3 HRQoL domains: physical functioning (PF), Global Health Status/Quality of Life (GHS/QoL) and abdominal pain and discomfort (OG25-Pain). PF and GHS/QoL were collected in the EORTC QLQ-C30. OG25-Pain was collected in the EORTC QLQ-OG25.

	Secondary Endpoint	ORR	The proportion of participants who had a BOR of CR or PR assessed by IRC per RECIST 1.1.
	Secondary Endpoint	DOR	Time from the date of the first response (CR or PR) until the date of radiological disease progression assessed by IRC per RECIST 1.1 or date of death from any cause, whichever was earliest.
	Secondary Endpoint	HRQoL	HRQoL endpoints collected via the EORTC QLQ-C30, QLQ-OG25, global pain (GP) and EQ-5D-5L questionnaires.

Notes	CLDN18.2-positive was defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining, determined by central immunohistochemistry testing.
Database Lock (data cutoff date)	09 Sep 2022
Results and Analysis	
Analysis Description	**Primary Analysis (PFS)**
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (09 Sep 2022)

Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
	Number of Participants	283	282
	PFS events, n (%)	146 (51.6)	167 (59.2)
	Censored, n (%)	137 (48.4)	115 (40.8)
	Duration of PFS (months)†		
	Median (95% CI)	10.61 (8.90, 12.48)	8.67 (8.21, 10.28)
	Range‡	0.03+, 40.15+	0.03+, 31.90+
	Stratified Analysis§		
	1-sided P value¶	0.0066	
	Hazard ratio (95% CI)††	0.751 (0.598, 0.942)	
	Median Follow-up Time (months)‡‡	12.94 (11.63, 15.28)	12.65 (10.71, 15.24)
	PFS Rate, % (95% CI)§§		
	At 6 months	78.05 (72.43, 82.67)	71.95 (66.03, 77.03)
	At 12 months	48.86 (41.92, 55.43)	35.04 (28.45, 41.69)
	At 18 months	30.93 (23.83, 38.28)	20.82 (14.48, 27.96)

Notes	† Based on Kaplan-Meier estimate. ‡ + indicates censoring. § Stratification factors were region, number of organs with metastatic sites, and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test. †† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm. ‡‡ Based on reverse Kaplan-Meier estimate. §§ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.
Analysis Description	**Key Secondary Analysis (OS)**
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (09 Sep 2022)

Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
	Number of Participants	283	282
	Deaths, n (%)	149 (52.7)	177 (62.8)
	Censored, n (%)	134 (47.3)	105 (37.2)
	Duration of Overall Survival (months)†		
	Median (95% CI)	18.23 (16.43, 22.90)	15.54 (13.47, 16.53)
	Range‡	0.03+, 42.09+	0.07, 36.90+

	Stratified Analysis§		
	1-sided P value¶	0.0053	
	Hazard ratio (95% CI)††	0.750 (0.601, 0.936)	
	Median Follow-up Time (months)‡‡	22.14 (18.04, 24.77)	20.93 (19.61, 25.66)
	OS Rate, % (95% CI)§§		
	At 12 months	67.69 (61.49, 73.12)	59.97 (53.63, 65.72)
	At 18 months	50.46 (43.51, 57.00)	38.05 (31.52, 44.54)
	At 24 months	38.77 (31.62, 45.85)	28.38 (22.10, 34.98)
Notes	† Based on Kaplan-Meier estimate. ‡ + indicates censoring. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test. †† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm. ‡‡ Based on reverse Kaplan-Meier estimate. §§ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.		
Analysis Description	**Key Secondary Analysis (TTCD)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (09 Sep 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
	Number of Participants	283	282
	Physical Functioning (Deterioration Threshold = 13†)		
	Total participants, n (%)	283 (100.0)	282 (100.0)
	Deterioration events, n (%)	115 (40.6)	102 (36.2)
	Censored, n (%)	168 (59.4)	180 (63.8)
	Time to First Confirmed Physical Functioning Deterioration (months)‡		
	Median (95% CI)	10.71 (6.01, NE)	12.32 (9.26, NE)
	Stratified analysis§		
	1-sided P value¶	0.0252	
	Hazard ratio (95% CI)††	1.309 (1.000, 1.713)	
	OG25-Pain (Deterioration Threshold = 16.7†)		
	Total participants, n (%)	283 (100.0)	282 (100.0)
	Deterioration events, n (%)	38 (13.4)	54 (19.1)
	Censored, n (%)	245 (86.6)	228 (80.9)
	Time to First Confirmed OG-25-Pain Deterioration (months)‡		
	Median (95% CI)	Not yet reached	Not yet reached (15.08, NE)
	Stratified analysis§		
	1-sided P value¶	0.0345	
	Hazard ratio (95% CI)††	0.679 (0.446, 1.034)	
	GHS/QoL (Deterioration Threshold = 13†)		
	Total participants, n (%)	283 (100.0)	282 (100.0)
	Deterioration events, n (%)	111 (39.2)	105 (37.2)
	Censored, n (%)	172 (60.8)	177 (62.8)
	Time to First Confirmed GHS/QoL Deterioration (months)‡		
	Median (95% CI)	15.44 (6.90, 22.83)	11.83 (8.74, 15.08)
	Stratified analysis§		
	1-sided P value¶	0.1321	
	Hazard ratio (95% CI)††	1.168 (0.890, 1.533)	
Notes	† The threshold values of 13 for Physical Functioning and GHS/QoL are based on Cocks et al (2012) and the threshold value of 16.7 for OG25-Pain is based on Norman et al (2003) and Sloan et al (2005).		

	‡ Time to confirmed deterioration = date of first confirmed clinically meaningful deterioration/censored date – randomization date + 1. *Footnotes continued on next page* § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. ¶ Based on 1-sided stratified log-rank test. †† Based on stratified Cox proportional hazard model with region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.		
Analysis Description	**Secondary Analysis (ORR)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (09 Sep 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
	Number of Participants	283	282
	Best overall response, n (%)†	256 (90.5)	266 (94.3)
	CR	19 (6.7)	10 (3.5)
	PR	116 (41.0)	124 (44.0)
	Stable disease	45 (15.9)	52 (18.4)
	Non-CR/non-progressive disease	52 (18.4)	59 (20.9)
	Progressive disease	15 (5.3)	17 (6.0)
	Not evaluable	4 (1.4)	3 (1.1)
	No disease	5 (1.8)	1 (0.4)
	Not available‡	27	16
	ORR, n (%)	135 (47.7)	134 (47.5)
	95% CI for ORR (%)§	(41.76, 53.70)	(41.56, 53.52)
	Stratified 1-sided P value¶	0.4875	
	DCR, n (%)††	232 (82.0)	245 (86.9)
	95% CI for ORR (%)§	(77.00, 86.28)	(82.37, 90.59)
	Stratified 1-sided P value¶	0.0569	
Notes	† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) was believed to be best response, the assessment should have been at least 8 weeks after randomization. For calculation of percentages, the denominator included the total number of participants in each arm. ‡ No post baseline imaging assessment. § Using exact method based on binomial distribution (Clopper-Pearson). ¶ Based on 1-sided Cochran-Mantel-Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. †† DCR was defined as the proportion of participants who had a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).		
Analysis Description	**Secondary Analysis (DOR)**		
Analysis Population and Time Point Description	FAS - All Objective Responders As of data cutoff date (09 Sep 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
	Number of Participants	135	134
	Events, n (%)	67 (49.6)	77 (57.5)
	Censored, n (%)	68 (50.4)	57 (42.5)
	Duration of Response (months)†		
	Median (95% CI)	9.00 (6.87, 10.25)	8.05 (6.47, 10.81)
	Range‡	0.03+, 38.08+	0.03+, 27.83+
	Stratified Analysis§		
	1-sided P value¶	0.2218	
	Hazard ratio (95% CI)††	0.876 (0.623, 1.233)	
Notes	† Based on Kaplan-Meier estimate. *Footnotes continued on next page* ‡ + indicates censoring.		

	§ Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test †† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.
Analysis Description	**Secondary Analysis (HRQoL)**
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (09 Sep 2022)
Notes	The secondary HRQoL endpoints collected via the EORTC QLQ-C30, QLQ-OG25, GP and EQ 5D-5L were analyzed with summary of change from baseline over time through the end of mFOLFOX6 treatment and inferential methods. The compliance rate for PRO completion was 71.0% or greater (range: 71.0% to 100%) for any treatment visits where there were more than 50 participants remaining on the study. The compliance rates were similar between the treatment arms during the treatment and follow-up periods of the study though no formal statistical testing was performed on these descriptive summary measures. Baseline total scores and subscale scores were comparable between the treatment arms. The confidence intervals of the total and subscale mean scores overlapped between the treatment groups for most visits during the treatment and follow-up periods though no formal statistical testing was performed on these descriptive summary measures.

Table 71: Summary of efficacy for trial 8951-CL-0302 (GLOW)

Title: A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared with Placebo Plus CAPOX as First-line Treatment of Subjects with Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma			
Study Identifier	ISN/Protocol 8951-CL-0302 EudraCT 2018-000519-26		
Design	Global, multi-center, double-blind, 1:1 randomized, placebo-controlled phase 3 study		
	Duration of Main Phase:		From 28 Nov 2018 to 07 Oct 2022 (data cutoff date)
	Duration of Run-in Phase:		Not Applicable
	Duration of Extension Phase:		Not Applicable
Hypothesis	Superiority		
Treatments Groups	**Arm A**	Zolbetuximab + CAPOX n = 254	
	Arm B	Placebo + CAPOX n = 253	
Endpoints and Definitions	Primary Endpoint	PFS	PFS assessed by blinded IRC. Time from date of randomization until the date of radiological disease progression assessed by IRC per RECIST 1.1 or death from any cause, whichever was earliest.
	Key Secondary Endpoint	OS	Time from the date of randomization until the date of death from any cause
	Key Secondary Endpoint	TTCD	Time to first confirmed deterioration, i.e., time from randomization to first clinically meaningful deterioration that was confirmed at the next scheduled visit. TTCD was defined for the following 3 HRQoL domains: physical functioning (PF), Global Health Status/Quality of Life (GHS/QoL) and abdominal pain and discomfort (OG25-Pain). PF and GHS/QoL were collected in the EORTC QLQ-C30. OG25-Pain was collected in the EORTC QLQ-OG25 plus STO22 Belching subscale.
	Secondary endpoint	ORR	The proportion of participants who had a BOR of CR or PR assessed by IRC per

			RECIST 1.1.
	Secondary endpoint	DOR	Time from the date of the first response (CR or PR) until the date of radiological disease progression assessed by IRC per RECIST 1.1 or date of death from any cause, whichever was earliest.
	Secondary endpoint	HRQoL	HRQoL endpoints collected via the EORTC QLQ-C30, QLQ-OG25 plus STO22 Belching subscale, global pain (GP) and EQ-5D-5L questionnaires.
Notes	CLDN18.2-positive was defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining, determined by central immunohistochemistry testing.		
Database Lock (data cutoff date)	07 Oct 2022		
Results and Analysis			
Analysis Description	**Primary Analysis (PFS)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (07 Oct 2022)		

Descriptive Statistics and Estimate Variability

Treatment Group	Zolbetuximab + CAPOX	Placebo + CAPOX
Number of Participants	254	253
PFS events, n (%)	137 (53.9)	172 (68.0)
Censored, n (%)	117 (46.1)	81 (32.0)
Duration of PFS (months)†		
Median (95% CI)	8.21 (7.46, 8.84)	6.80 (6.14, 8.08)
Range‡	0.03+, 29.01+	0.03+, 30.49
Stratified Analysis§		
1-sided P value¶	0.0007	
Hazard ratio (95% CI)††	0.687 (0.544, 0.866)	
Median Follow-up Time (months)‡‡	12.62 (10.32, 15.21)	12.09 (10.25, 15.05)
PFS Rate, % (95% CI)§§		
At 6 months	70.20 (63.42, 75.96)	61.47 (54.82, 67.45)
At 12 months	34.86 (27.75, 42.05)	19.13 (13.50, 25.51)
At 18 months	23.91 (17.09, 31.38)	10.62 (5.68, 17.33)

Notes

† Based on Kaplan-Meier estimate.

‡ + indicates censoring.

§ Stratification factors were region, number of organs with metastatic sites, and prior gastrectomy from the interactive response technology.

¶ Based on 1-sided log-rank test.

†† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

‡‡ Based on reverse Kaplan-Meier estimate.

§§ PFS rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Analysis Description	**Key Secondary Analysis (OS)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (07 Oct 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + CAPOX	Placebo + CAPOX
	Number of Participants	254	253
	Deaths, n (%)	144 (56.7)	174 (68.8)
	Censored, n (%)	110 (43.3)	79 (31.2)
	Duration of Overall Survival (months)†		
	Median (95% CI)	14.39 (12.29, 16.49)	12.16 (10.28, 13.67)
	Range‡	0.03+, 35.81+	0.03+, 33.84+
	Stratified Analysis§		
	1-sided P value¶	0.0118	
	Hazard ratio (95% CI)††	0.771 (0.615, 0.965)	
	Median Follow-up Time (months)‡‡	17.71 (16.33, 19.91)	18.43 (17.48, 20.80)
	OS Rate, % (95% CI)§§		
	At 12 months	57.54 (50.71, 63.77)	50.79 (44.12, 57.06)
	At 18 months	38.10 (30.96, 45.19)	28.14 (21.95, 34.65)
	At 24 months	28.92 (21.75, 36.46)	17.38 (11.62, 24.12)
Notes	† Based on Kaplan-Meier estimate. *Footnotes continued on next page* ‡ + indicates censoring. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. ¶ Based on 1-sided log-rank test. †† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm. ‡‡ Based on reverse Kaplan-Meier estimate. §§ Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.		
Analysis Description	**Key Secondary Analysis (TTCD)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (07 Oct 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + CAPOX	Placebo + CAPOX
	Number of Participants	254	253
	Physical Functioning (Deterioration Threshold = 13†)		
	Total participants, n (%)	254 (100.0)	253 (100.0)
	Deterioration events, n (%)	99 (39.0)	109 (43.1)
	Censored, n (%)	155 (61.0)	144 (56.9)
	Time to First Confirmed Physical Functioning Deterioration (months)‡		
	Median (95% CI)	8.31 (5.88, 19.81)	7.92 (6.47, 11.10)
	Stratified analysis§		
	1-sided P value¶	0.4980	
	Hazard ratio (95% CI)††	0.999 (0.759, 1.315)	
	OG25-Pain (Deterioration Threshold = 16.7†)		
	Total participants, n (%)	254 (100.0)	253 (100.0)
	Deterioration events, n (%)	44 (17.3)	40 (15.8)
	Censored, n (%)	210 (82.7)	213 (84.2)
	Time to First Confirmed OG-25-Pain Deterioration (months)‡		
	Median (95% CI)	Not yet reached	25.82 (NE, NE)
	Stratified analysis§		
	1-sided P value¶	0.3880	
	Hazard ratio (95% CI)††	1.066 (0.692, 1.642)	
	GHS/QoL (Deterioration Threshold = 13†)		

	Total participants, n (%)	254 (100.0)	253 (100.0)
	Deterioration events, n (%)	85 (33.5)	111 (43.9)
	Censored, n (%)	169 (66.5)	142 (56.1)
	Time to First Confirmed GHS/QoL Deterioration (months)‡		
	Median (95% CI)	9.69 (7.39, NE)	7.49 (6.11, 9.86)
	Stratified analysis§		
	1-sided P value¶	0.1299	
	Hazard ratio (95% CI)††	0.847 (0.636, 1.129)	
Notes	† The threshold values of 13 for Physical Functioning and GHS/QoL are based on Cocks et al (2012) and the threshold value of 16.7 for OG25-Pain is based on Norman et al (2003) and Sloan et al (2005). ‡ Time to confirmed deterioration = date of first confirmed clinically meaningful deterioration/censored date – randomization date + 1. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. ¶ Based on 1-sided stratified log-rank test. *Footnotes continued on next page* †† Based on stratified Cox proportional hazard model with region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.		
Analysis Description	**Secondary Analysis (ORR)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (07 Oct 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + CAPOX	Placebo + CAPOX
	Number of Participants	254	253
	Best overall response, n (%)†	210 (82.7)	226 (89.3)
	CR	9 (3.5)	5 (2.0)
	PR	99 (39.0)	97 (38.3)
	Stable disease	46 (18.1)	57 (22.5)
	Non-CR/non-progressive disease	40 (15.7)	33 (13.0)
	Progressive disease	11 (4.3)	28 (11.1)
	Not evaluable	1 (0.4)	5 (2.0)
	No disease	4 (1.6)	1 (0.4)
	Not available‡	44	27
	ORR, n (%)	108 (42.5)	102 (40.3)
	95% CI for ORR (%)§	(36.36, 48.85)	(34.22, 46.64)
	Stratified 1-sided P value¶	0.3104	
	DCR, n (%)††	194 (76.4)	192 (75.9)
	95% CI for ORR (%)§	(70.67, 81.46)	(70.13, 81.03)
	Stratified 1-sided P value¶	0.4609	
Notes	† The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) was believed to be best response, the assessment should have been at least 8 weeks after randomization. For calculation of percentages, the denominator included the total number of participants in each arm. ‡ No post baseline imaging assessment. § Using exact method based on binomial distribution (Clopper-Pearson). ¶ Based on 1-sided Cochran-Mantel-Haenszel test. Stratification factors were region, number of organs with metastatic sites and prior gastrectomy. †† DCR was defined as the proportion of participants who had a best overall response of CR, PR, stable disease or non-CR/non-progressive disease (≥ 8 weeks).		
Analysis Description	**Secondary Analysis (DOR)**		
Analysis Population and Time Point Description	FAS - All Objective Responders As of data cutoff date (07 Oct 2022)		
Descriptive Statistics and Estimate Variability	Treatment Group	Zolbetuximab + CAPOX	Placebo + CAPOX
	Number of Participants	108	102
	Events, n (%)	66 (61.1)	67 (65.7)
	Censored, n (%)	42 (38.9)	35 (34.3)

	Duration of Response (months)†		
	Median (95% CI)	6.14 (5.03, 8.08)	6.08 (4.44, 6.34)
	Range‡	0.03+, 26.94+	0.03+, 28.32
	Stratified Analysis§		
	1-sided P value¶	0.0673	
	Hazard ratio (95% CI)††	0.758 (0.527, 1.089)	
Notes	† Based on Kaplan-Meier estimate. ‡ + indicates censoring. § Stratification factors were region, number of organs with metastatic sites and prior gastrectomy from the interactive response technology. *Footnotes continued on next page* ¶ Based on 1-sided log-rank test †† Based on Cox proportional hazard model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in the hazard rate in favor of the treatment arm.		
Analysis Description	**Secondary Analysis (HRQoL)**		
Analysis Population and Time Point Description	FAS (all participants randomized to 1 of the treatment arms) As of data cutoff date (07 Oct 2022)		
Notes	The secondary HRQoL endpoints collected via the EORTC QLQ-C30, QLQ-OG25 plus STO22 Belching subscale, GP and EQ-5D-5L were analyzed with summary of change from baseline over time through the end of CAPOX treatment and inferential methods. The compliance rate for PRO completion was 85.3% or greater (range: 85.3% to 100%) for any treatment visits where there were more than 50 participants remaining on the study. The compliance rates were similar between the treatment arms during the treatment and follow-up periods of the study though no formal statistical testing was performed on these descriptive summary measures. Baseline total scores and subscale scores were comparable between the treatment arms. The confidence intervals of the total and subscale mean scores overlapped between the treatment groups for most visits during the treatment and follow-up periods though no formal statistical testing was performed on these descriptive summary measures.		

2.6.5.5. Clinical studies in special populations

Data by **Age** groups

Table 72: Number (%) of Participants treated with zolbetuximab (in different dosing regimens) by Age Group (excerpt from Table 25 response to D120 LoQ)

Study	<65	65 - <75	75 - <85	≥ 85
SPOTLIGHT (8951-CL-0301)	168 (60.2%)	91 (32.6%)	20 (7.2%)	0
GLOW (8951-CL-0302)	167 (65.7%)	71 (28.0%)	16 (6.3%)	0
ILUSTRO (8951-CL-0103)	36 (66.7%)	16 (29.6%)	2 (3.7%)	0
8951-CL-0104	10 (55.6%)	6 (33.3%)	2 (11.1%)	0
8951-CL-0105	10 (83.3%)	2 (16.7%)	0	0
FIM (GM-IMAB-001)	8 (53.3%)	6 (40.0%)	1 (6.7%)	0
MONO (GM-IMAB-001-02)	38 (70.4%)	13 (24.1%)	3 (5.6%)	0
FAST (GM-IMAB-001-03)	125 (77.2%)	33 (20.4%)	4 (2.5%)	0
GM-IMAB-001-04	22 (78.6%)	5 (17.9%)	1 (3.6%)	0

2.6.5.6. In vitro biomarker test for patient selection for efficacy

CLDN18.2 is a highly cell type-specific differentiation antigen that is expressed by differentiated gastric mucosa cells in the pit and base regions of gastric glands and is not detectable in any other normal cell type of the human body at the transcript level nor as protein [Sahin et al, 2008]. CLDN18.2 is expressed in a number of human cancers including gastric and pancreatic adenocarcinomas [Lee et al, 2011]. CLDN18.2 is the dominant isoform of claudin-18 in gastric, GEJ and pancreatic cancers [Wöll et al, 2014; Niimi et al, 2001]. The expression of CLDN18.2 is retained upon malignant transformation of gastric epithelia and is present in approximately 80% of primary gastric adenocarcinomas ([Sahin et al, 2008] and Astellas data on file). CLDN18.2 expression was detected in diffuse and intestinal gastric adenocarcinomas [Sahin et al, 2008]. CLDN18.2 is also expressed in lymph node metastases of gastric adenocarcinomas and in distant metastases, including bile duct, lung and the ovary (Krukenberg tumors). There are no currently approved treatments specifically targeting CLDN18.2-positive gastric/GEJ cancer.

Zolbetuximab (IMAB362) is a genetically engineered, highly purified chimeric (mouse/human IgG1) antibody targeted against the tight junction molecule CLDN18.2.

Zolbetuximab recognizes the first extracellular domain of CLDN18.2 with high affinity and specificity. Zolbetuximab does not bind to the closely related CLDN18.1 isoform nor does it bind to any other claudin family protein.

Companion Diagnostic Assay Development

A key inclusion criterion for patient enrollment in the zolbetuximab clinical development program has been to demonstrate CLDN18.2 positivity in patients' tumor tissue by IHC assessment.

Eligibility for enrollment in the SPOTLIGHT and GLOW studies was determined on tumor tissue samples using the investigational VENTANA CLDN18 (43-14A) RxDx Assay. VENTANA CLDN18 (43-14A) RxDx Assay is a GMP manufactured automated IHC assay that has been developed as a companion diagnostic assay with a defined IHC interpretation and cutoff to aid in identifying patients with gastric or GEJ adenocarcinoma eligible for treatment with Vyloy (zolbetuximab).

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

Patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive (defined as ≥75% viable tumour cells (%TC) demonstrating moderate to strong membranous CLDN18 staining) as determined by a validated test, who are eligible for treatment with Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy

The safety and efficacy of Vyloy in combination with chemotherapy was evaluated in two phase 3, double-blind, randomised, multicentre studies that enrolled 1072 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

CLDN18.2 positivity (defined as ≥75% viable tumour cells (%TC) demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GEJ tumour tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay performed in a central laboratory.

VENTANA CLDN18 (43-14A) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-claudin 18, clone 43-14A, intended for laboratory use in the assessment of claudin 18 (CLDN18) protein in formalin-fixed, paraffin-embedded (FFPE) gastric adenocarcinoma including gastroesophageal junction (GEJ) tissue specimens by light microscopy. This assay is used with OptiView DAB IHC Detection Kit for staining on a BenchMark IHC/ISH instrument.

The assay is indicated as a companion diagnostic to aid in identifying patients with gastric or GEJ adenocarcinoma who may be eligible for treatment with Vyloy (zolbetuximab) in accordance with the approved therapeutic product labeling. The clinical cutoff for the therapeutic product is ≥ 75% viable tumor cells (% TC) demonstrating moderate to strong membrane CLDN18 staining above background.

CLDN18 is expressed as two protein isoforms: CLDN18.1 and CLDN18.2. Both isoforms are 261 amino acids in length; CLDN18.1 differs from CLDN18.2 in the N-terminal amino acids.

The primary antibody used in the VENTANA CLDN18 (43-14A) RxDx Assay targets the conserved C-terminus region of the CLDN18 protein and detects both CLDN18.1 and CLDN18.2.

CLDN18.1 is predominantly expressed in normal and neoplastic lung tissue. CLDN18.2 is only expressed in differentiated epithelial cells of the gastric mucosa and not in other healthy tissues under normal physiological conditions. Under malignant transformation, CLDN18.2 is frequently retained in gastric cancer (GC) and its metastases and may be expressed in other neoplastic tissues (e.g. pancreas, lung, ovary). Expression of CLDN18.2 in various solid tumors (e.g. gastric, pancreas) has been reported to be associated with loss of cell-cell adhesion, epithelial-mesenchymal transition, and tumor progression and metastasis.

The applicant seeks for approval of Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are *Claudin (CLDN) 18.2 positive.* Therefore, a CDx should be available at the time of the marketing authorisation.

The conformity assessment CE mark submission (Assessment of Technical Documentation) for the CDx was submitted by Ventana/Roche Diagnostics to the notified body under the 2017/746 IVDR regulation; a positive CHMP opinion was provided by EMA via the EMA consultation process on 26th July 2024. A CE marked certificate for the CDx will be awarded by the Notified body upon completion of its review.

Vyloy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-esophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive. CLDN18.2 positivity is determined by immunohistochemistry with the VENTANA CLDN18 (43-14A) RxDx Assay.

VENTANA CLDN18 (43-14A) RxDx Assay

The analytical and clinical performance of the device has been demonstrated and key information about the safety and performance of the device will be available in the Summary of Safety and Performance (SSP) of the VENTANA CLDN18 (43-14A) RxDx Assay upon CE marking.

Analytical Performance - Refer to the VENTANA CLDN18 (43-14A) RxDx Assay Summary of Safety and Performance (SSP).

Clinical Performance – GC/GEJ Adenocarcinoma - Refer to the VENTANA CLDN18 (43-14A) RxDx Assay Summary of Safety and Performance (SSP) and section 5.1 of the Vyloy SmPC.

HR b (95% CI)	0.687 (0.544, 0.866)
P-value c	0.0007

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Cut-point selection

In studies SPOTLIGHT and GLOW only CLDN18.2 positive patients were included. CLDN18.2-positive tumours were defined as ≥ 75% of tumour cells having moderate to strong membranous CLDN18 staining based on IHC (referred to as ≥ 75% cutoff hereafter) using the CLDN18 RxDx Assay.

The FAST study evaluating the efficacy and safety of zolbetuximab in combination with EOX compared with EOX alone was intended to identify a patient population most likely to benefit from addition of zolbetuximab to fluoropyrimidine- and platinum-containing chemotherapy, with favourable results for median PFS and median OS.

Based on these results from FAST, the pivotal SPOTLIGHT and GLOW studies were designed to target a higher CLDN18.2 tumour testing cutoff.

Table 75: Prevalence of CLDN18.2 Positivity by Region in SPOTLIGHT and GLOW Studies

Parameter Category/Statistic	Number of Unique Screened Participants with Valid CLDN18 IHC Results	≥ 75% (moderate/strong staining)
SPOTLIGHT		
All	2403	922 (38.4)
Region		
Asia Pacific (excluding China)	664	224 (33.7)
North America	430	163 (37.9)
China Mainland	159	57 (35.8)
South America	298	98 (32.9)
Europe/Middle East	852	380 (44.6)
GLOW		
All	2104	808 (38.4)
Region		
Asia Pacific (excluding China)	650	255 (39.2)
North America	55	20 (36.4)
China Mainland	685	238 (34.7)
South America	42	4 (9.5)
Europe/Middle East	672	291 (43.3)

CLDN18: claudin-18; CLDN18.2: claudin-18.2; IHC: immunohistochemistry.

Correlation of CLDN18.2 Expression and Clinical Outcome (FAST study)

Progression-free Survival

For participants with ≥ 70% of tumour cells staining for CLDN18.2 at baseline, the median PFS was 3.3 months longer in Arm 2 compared with Arm 1 (9.0 vs 5.7 months, respectively), with an HR of 0.38 (95% CI: 0.23, 0.62) [**Table 78**]. The median PFS was numerically longer in Arm 3 compared with Arm 1 (6.3 vs 5.7 months, respectively). The HR was favourable, but the CI included 1 (HR = 0.68 [95% CI: 0.44, 1.05]).

For participants with < 70% of tumour cells staining for CLDN18.2 at baseline (63 participants in total, 25 in Arm 1, 20 in Arm 2, and 18 in Arm 3), the median PFS was similar in Arm 2 compared with Arm 1 (4.3 vs 4.1 months, respectively). The HR was favourable, but the 95% CI included 1 (HR = 0.71

[95% CI: 0.32, 1.57]). A more favourable effect was observed when comparing Arm 3 with Arm 1 in this subgroup of participants. The median PFS was 3.3 months longer in Arm 3 compared with Arm 1 (7.4 vs 4.1 months), with an HR of 0.32 (95% CI: 0.14, 0.78).

Overall Survival

For participants with ≥ 70% of tumour cells staining for CLDN18.2 at baseline, the median OS was 7.6 months longer in Arm 2 compared with Arm 1 (16.5 vs 8.9 months, respectively), with an HR of 0.50 (95% CI: 0.33, 0.74). The median OS was numerically longer in Arm 3 compared with Arm 1 (9.4 vs 8.9 months, respectively). The HR was favourable, but the 95% CI included 1 (HR = 0.82 [95% CI: 0.57, 1.18]).

For participants with < 70% of tumour cells staining for CLDN18.2 at baseline (63 participants in total, 25 in Arm 1, 20 in Arm 2, and 18 in Arm 3), the median OS was numerically longer in Arm 2 compared with Arm 1 (8.3 vs 7.4 months, respectively). The HR was favourable, but the CI included 1 (HR = 0.78 [95% CI: 0.40, 1.49]). Similarly, the median OS was numerically longer in Arm 3 compared with Arm 1 (10.4 vs 7.4 months, respectively), with an HR of 0.57 (95% CI: 0.29, 1.11).

Table 76: PFS (IRC) and OS in Participants with Tumours with ≥ 70% CLDN18.2 Expression – FAS (FAST)

Category Parameter/Statistics		PFS CLDN18.2 Staining in ≥ 70% of Cells			OS CLDN18.2 Staining in ≥ 70% of Cells		
		Arm 1 EOX Alone (n = 59)	Arm 2 Zolbetuximab 800/600 mg/m² plus EOX (n = 57)	Arm 3 Zolbetuximab 1000 mg/m² plus EOX (n = 67)	Arm 1 EOX Alone (n = 59)	Arm 2 Zolbetuximab 800/600 mg/m² plus EOX (n = 57)	Arm 3 Zolbetuximab 1000 mg/m² plus EOX (n = 67)
Censoring summary†, n (%)							
Participants with event		46 (78.0)	31 (54.4)	38 (56.7)	56 (94.9)	47 (82.5)	62 (92.5)
Censored participants		13 (22.0)	26 (45.6)	29 (43.3)	3 (5.1)	10 (17.5)	5 (7.5)
Kaplan-Meier estimates, months							
25th percentile (95% CI)		2.8 (1.7, 4.3)	5.2 (4.2, 7.1)	4.3 (2.8, 5.6)	5.6 (2.4, 7.1)	8.3 (5.7, 10.4)	7.2 (5.3, 7.9)
Median (95% CI)		5.7 (4.3, 7.2)	9.0 (7.1, 12.4)	6.3 (5.5, 8.0)	8.9 (7.1, 11.0)	16.5 (10.4, 22.6)	9.4 (8.3, 12.8)
75th percentile (95% CI)		8.0 (7.2, 9.8)	20.0 (11.6, NA)	9.8 (7.6, 13.9)	13.4 (11.0, 17.4)	30.4 (22.6, 43.0)	16.2 (12.8, 22.7)
PFS or OS rate	12 months	5.1%	39.8%	16.3%	31.8%	61.9%	38.6%
	18 months	2.5%	33.7%	9.8%	10.6%	47.4%	24.7%
	24 months	0	18.4%	9.8%	7.1%	35.9%	13.9%
Treatment Comparison vs EOX Alone							
Hazard ratio (95% CI)‡		NA	0.38 (0.23, 0.62)	0.68 (0.44, 1.05)	NA	0.50 (0.33, 0.74)	0.82 (0.57, 1.18)
Log-rank test P value§			< 0.0005	0.1285		< 0.0005	0.3930
Treatment Comparison vs Zolbetuximab 1000 mg/m² plus EOX							
Hazard ratio (95% CI)‡		NA	0.56 (0.34, 0.92)	NA	NA	0.61 (0.41, 0.90)	NA
Log-rank test P value§			0.0365			0.0248	

Data cutoff: 31 Jan 2019.

Table 77: PFS (Independent Reviewer) by CLDN18.2 Expression Category – Primary Analysis

Category / Parameter/Statistics		CLDN18.2 Staining in < 70% of Cells				CLDN18.2 Staining in ≥ 70% of Cells			
		Arm 1 (n = 25)	Arm 2 (n = 20)	Arm 3 (n = 18)	Total Zolbetuximab (n = 38)	Arm 1 (n = 59)	Arm 2 (n = 57)	Arm 3 (n = 67)	Total Zolbetuximab (n = 124)
Censoring summary†, n (%)									
Patients with event		16 (64.0)	11 (55.0)	11 (61.1)	22 (57.9)	46 (78.0)	31 (54.4)	38 (56.7)	69 (55.6)
Censored patients		9 (36.0)	9 (45.0)	7 (38.9)	16 (42.1)	13 (22.0)	26 (45.6)	29 (43.3)	55 (44.4)
Kaplan-Meier estimates, months									
25th percentile (95% CI)		1.7 (0.6, 3.8)	2.8 (1.5, 4.3)	4.6 (1.4, 7.4)	4.2 (1.5, 4.6)	2.8 (1.7, 4.3)	5.2 (4.2, 7.1)	4.3 (2.8, 5.6)	4.4 (4.2, 5.6)
Median (95% CI)		4.1 (1.9, 7.1)	4.3 (1.5, 5.7)	7.4 (4.5, 9.3)	5.6 (4.3, 8.4)	5.7 (4.3, 7.2)	9.0 (7.1, 12.4)	6.3 (5.5, 8.0)	7.5 (5.9, 9.0)
75th percentile (95% CI)		7.1 (4.3, 7.4)	5.7 (4.3, 9.2)	9.3 (5.8, NA)	9.0 (5.7, 20.0)	8.0 (7.2, 9.8)	18.3 (11.6, NA)	9.8 (7.6, 13.9)	12.4 (9.8, 20.0)
PFS rate	12 months	0	0	18.0%	10.7%	5.1%	38.2%	16.3%	26.9%
	18 months	0	0	18.0%	10.7%	2.5%	31.8%	9.8%	20.6%
	24 months	0	0	9.0%	5.4%	0	14.8%	9.8%	12.0%
Treatment comparison vs Arm 1									
Hazard ratio (95% CI)‡		NA	0.71 (0.32, 1.57)	0.32 (0.14, 0.78)	0.48 (0.24, 0.97)	NA	0.40 (0.25, 0.65)	0.68 (0.44, 1.05)	0.52 (0.35, 0.77)
Log-rank test P value§			0.4968	0.0097	0.0345		< 0.0005	0.1285	0.0010
Treatment comparison vs Arm 3									
Hazard ratio (95% CI)‡		NA	2.19 (0.89, 5.39)	NA	NA	NA	0.59 (0.36, 0.96)	NA	NA
Log-rank test P value§			0.0978				0.0519		

All patients who were randomized and who received at least 1 dose of any study medication (FAS)

Arm 1: EOX; Arm 2: EOX + zolbetuximab 800/600 mg/m²; Arm 3: EOX + zolbetuximab 1000 mg/m²; Total zolbetuximab: EOX + zolbetuximab 800/600 + 1000 mg/m²

The primary analysis of efficacy endpoints was based on the data cutoff date of 18 Dec 2015.

PFS was defined as the time from randomization to the first observation of PD (based on central reading by an independent reviewer) or death from any cause.

CI: confidence interval; CLDN18.2: claudin-18 splice variant 2; EOX: epirubicin, oxaliplatin and capecitabine; FAS: full analysis set; NA: not applicable; PD: progressive disease; PFS: progression-free survival

† Patients who did not have documented PD or death were censored as of the last tumor evaluation when they were alive and progression-free.

‡ Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline.

Footnotes continued on next page

Table 78: OS by CLDN18.2 Expression Category – Primary Analysis

Category / Parameter/Statistics		CLDN18.2 Staining in < 70% of Cells				CLDN18.2 Staining in ≥ 70% of Cells			
		Arm 1 (n = 25)	Arm 2 (n = 20)	Arm 3 (n = 18)	Total Zolbetuximab (n = 38)	Arm 1 (n = 59)	Arm 2 (n = 57)	Arm 3 (n = 67)	Total Zolbetuximab (n = 124)
Censoring summary†, n (%)									
Patients with event		23 (92.0)	16 (80.0)	14 (77.8)	30 (78.9)	52 (88.1)	38 (66.7)	55 (82.1)	93 (75.0)
Censored patients		2 (8.0)	4 (20.0)	4 (22.2)	8 (21.1)	7 (11.9)	19 (33.3)	12 (17.9)	31 (25.0)
Kaplan-Meier estimates, months									
25th percentile (95% CI)		4.5 (0.6, 6.4)	6.9 (1.5, 8.2)	8.1 (4.5, 9.7)	6.9 (4.5, 8.3)	5.6 (2.4, 7.1)	8.3 (5.7, 10.4)	7.2 (5.3, 7.9)	7.4 (6.0, 8.3)
Median (95% CI)		7.4 (4.5, 10.2)	8.3 (6.2, 11.6)	10.4 (5.2, 18.7)	9.0 (7.8, 10.4)	8.9 (7.1, 11.0)	16.5 (10.4, 21.7)	9.4 (8.3, 12.8)	11.7 (9.4, 13.7)
75th percentile (95% CI)		10.9 (7.7, 13.4)	11.6 (8.3, 18.7)	22.2 (10.4, NA)	13.1 (10.3, 24.2)	13.4 (11.0, 17.4)	NA (21.7, NA)	16.2 (12.8, 22.7)	22.6 (20.1, NA)
Overall survival rate	12 months	16.8%	23.7%	32.1%	27.8%	31.8%	61.9%	38.6%	49.3%
	18 months	8.4%	11.8%	32.1%	21.6%	10.6%	47.4%	24.7%	35.1%
	24 months	8.4%	5.9%	19.3%	12.4%	8.8%	34.2%	11.2%	22.4%
Treatment comparison vs Arm 1									
Hazard ratio (95% CI)‡		NA	0.78 (0.40, 1.50)	0.55 (0.28, 1.10)	0.66 (0.37, 1.15)	NA	0.45 (0.30, 0.69)	0.84 (0.57, 1.23)	0.62 (0.44, 0.87)
Log-rank test P value§			0.4008	0.1212	0.1370		< 0.0005	0.3044	0.0074
Treatment comparison vs Arm 3									
Hazard ratio (95% CI)‡		NA	1.41 (0.68, 2.97)	NA	NA	NA	0.54 (0.35, 0.82)	NA	NA
Log-rank test P value§			0.2658				0.0033		

All patients who were randomized and who received at least 1 dose of any study medication (FAS)

Arm 1: EOX; Arm 2: EOX + zolbetuximab 800/600 mg/m²; Arm 3: EOX + zolbetuximab 1000 mg/m²; Total zolbetuximab: EOX + zolbetuximab 800/600 + 1000 mg/m²

The primary analysis of efficacy endpoints was based on the data cutoff date of 18 Dec 2015.

Overall survival was defined as the time from randomization to death from any cause or last contact, if alive.

CI: confidence interval; CLDN18.2: claudin-18 splice variant 2; EOX: epirubicin, oxaliplatin and capecitabine; FAS: full analysis set; NA: not applicable

† The censoring rules for the analysis of overall survival are provided in [Appendix 13.1.9, Statistical Analysis Plan, Section 7.7.2].

‡ Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline.

2.6.5.7. Analysis performed across trials (pooled analyses and meta-analysis)

An excerpt of baseline characteristics with differences notable between the SPOTLIGHT and GLOW studies (and pooled data across both studies) are shown in the following table:

Table 79: Summary of Demographics and Baseline Characteristics: Comparison Across SPOTLIGHT and GLOW – FAS (excerpt from Table 20 SCE and Table 8.2.2)

Parameter	SPOTLIGHT		GLOW		Integrated (SPOTLIGHT and GLOW)	
	Zolbetuximab plus mFOLFOX6 (n = 283)	Placebo plus mFOLFOX6 (n = 282)	Zolbetuximab plus CAPOX (n = 254)	Placebo plus CAPOX (n = 253)	Zolbetuximab plus mFOLFOX6 or CAPOX (n = 537)	Placebo plus mFOLFOX6 or CAPOX (n = 535)
Ethnicity, n (%)						
Hispanic or Latino	36 (13.8)	37 (14.8)	10 (4.0)	7 (2.8)	46 (9.0)	44 (8.8)
Race, n (%)						
Caucasian	140 (53.6)	134 (53.0)	94 (37.3)	90 (36.3)	234 (45.6)	224 (44.7)
Black or African American	5 (1.9)	2 (0.8)	0	0	5 (1.0)	2 (0.4)
Asian	96 (36.8)	97 (38.3)	158 (62.7)	158 (63.7)	254 (49.5)	255 (50.9)
American Indian or Alaska Native	9 (3.4)	8 (3.2)	0	0	9 (1.8)	8 (1.6)
Other	11 (4.2)	12 (4.7)	0	0	11 (2.1)	12 (2.4)
Missing	22	29	2	5	24	34
Weight, kg						
Median	63.00	64.80	60.50	59.55	61.20	61.05
Min, max	38.0, 110.6	28.5, 128.3	35.5, 111.2	29.1, 100.0	35.5, 111.2	28.5, 128.3
Geographical Region, n (%)						
Asia	88 (31.1)	89 (31.6)	157 (61.8)	158 (62.5)	245 (45.6)	247 (46.2)
Non-Asia	195 (68.9)	193 (68.4)	97 (38.2)	95 (37.5)	292 (54.4)	288 (53.8)
Medical condition						
Gastric adenocarcinoma	219 (77.4%)	210 (74.5%)	219 (86.2%)	209 (82.6%)	438 (81.6%)	419 (78.3%)
GEJ	64 (22.6%)	72 (25.5%)	35 (13.8%)	44 (17.4%)	99 (18.4%)	116 (21.7%)

Efficacy analysis of the SPOTLIGHT and GLOW studies and the integrated efficacy analysis of both studies are presented in the following table:

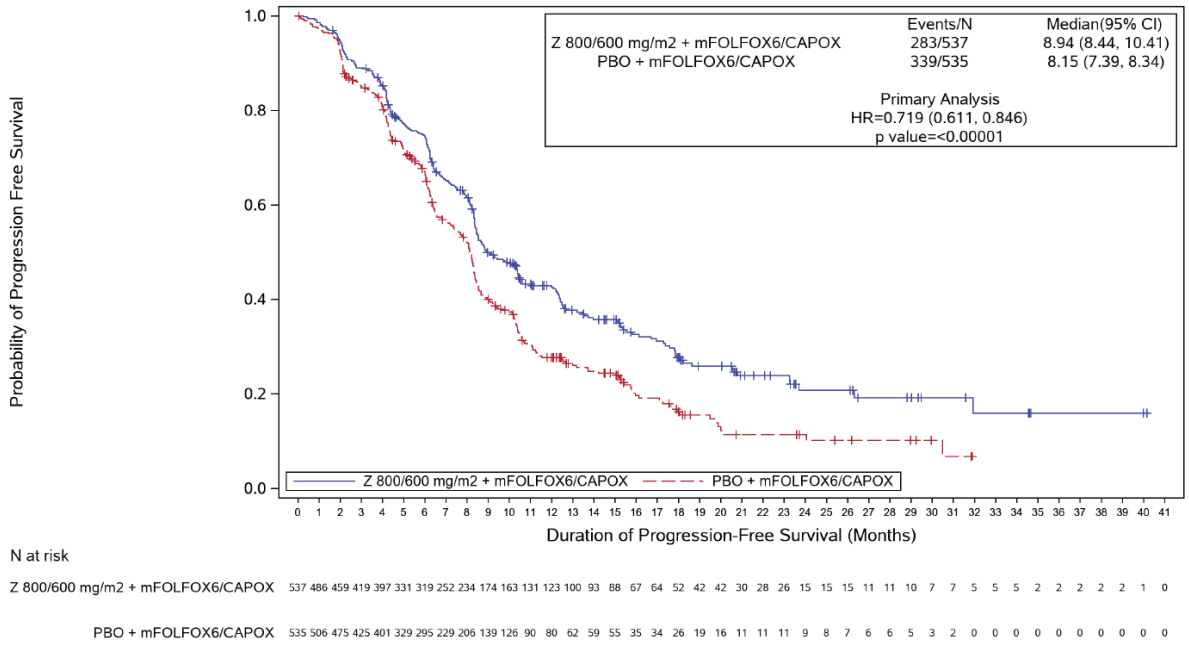
Table 80: Overview of Efficacy in SPOTLIGHT and GLOW and Integrated Efficacy Analysis

	SPOTLIGHT		GLOW		Integrated Efficacy Analysis (SPOTLIGHT and GLOW)	
Parameter	**Zolbetuximab plus mFOLFOX6 (n = 283)**	**Placebo plus mFOLFOX6 (n = 282)**	**Zolbetuximab plus CAPOX (n = 254)**	**Placebo plus CAPOX (n = 253)**	**Zolbetuximab plus mFOLFOX6 or CAPOX (n = 537)**	**Placebo plus mFOLFOX6 or CAPOX (n = 535)**
PFS (Assessed by IRC)						
Events, n (%)	146 (51.6)	167 (59.2)	137 (53.9)	172 (68.0)	283 (52.7)	339 (63.4)
Median duration, months (95% CI) †	10.61 (8.90, 12.48)	8.67 (8.21, 10.28)	8.21 (7.46, 8.84)	6.80 (6.14, 8.08)	8.94 (8.44, 10.41)	8.15 (7.39, 8.34)
HR (95% CI) ‡	0.751 (0.598, 0.942)		0.687 (0.544, 0.866)		0.719 (0.611, 0.846)	
P value§	0.0066		0.0007		< 0.00001	
Overall Survival						
Deaths, n (%)	149 (52.7)	177 (62.8)	144 (56.7)	174 (68.8)	293 (54.6)	351 (65.6)
Median duration, months (95% CI) †	18.23 (16.43, 22.90)	15.54 (13.47, 16.53)	14.39 (12.29, 16.49)	12.16 (10.28, 13.67)	16.49 (15.47, 17.87)	13.63 (12.22, 14.85)
HR (95% CI) ‡	0.750 (0.601, 0.936)		0.771 (0.615, 0.965)		0.760 (0.649, 0.890)	
P value§	0.0053		0.0118		0.0003	
TTCD						
Physical Functioning (Deterioration Threshold = 13) ¶						
Events (n, %)	115 (40.6)	102 (36.2)	99 (39.0)	109 (43.1)	214 (39.9)	211 (39.4)
Median TTCD, months††	10.71	12.32	8.31	7.92	9.69	9.72
HR (95% CI) ‡‡	1.309 (1.000, 1.713)		0.999 (0.759, 1.315)		1.147 (0.947, 1.390)	
OG25-Pain (Deterioration Threshold = 16.7) ¶						
Events (n, %)	38 (13.4)	54 (19.1)	44 (17.3)	40 (15.8)	82 (15.3)	94 (17.6)
Median TTCD, months††	NYR	NYR	NYR	25.82	NYR	25.82
HR (95% CI) ‡‡	0.679 (0.446, 1.034)		1.066 (0.692, 1.642)		0.844 (0.626, 1.139)	
GHS/QoL (Deterioration Threshold = 13) ¶						
Events (n, %)	111 (39.2)	105 (37.2)	85 (33.5)	111 (43.9)	196 (36.5)	216 (40.4)
Median TTCD, months††	15.44	11.83	9.69	7.49	10.61	9.36
HR (95% CI) ‡‡	1.168 (0.890, 1.533)		0.847 (0.636, 1.129)		1.003 (0.824, 1.221)	
Best Overall Response§§						
Evaluable, n (%)	256 (90.5)	266 (94.3)	210 (82.7)	226 (89.3)	466 (86.8)	492 (92.0)
CR	19 (6.7)	10 (3.5)	9 (3.5)	5 (2.0)	28 (5.2)	15 (2.8)
PR	116 (41.0)	124 (44.0)	99 (39.0)	97 (38.3)	215 (40.0)	221 (41.3)
SD	45 (15.9)	52 (18.4)	46 (18.1)	57 (22.5)	91 (16.9)	109 (20.4)
Non-CR/Non-PD	52 (18.4)	59 (20.9)	40 (15.7)	33 (13.0)	92 (17.1)	92 (17.2)
PD	15 (5.3)	17 (6.0)	11 (4.3)	28 (11.1)	26 (4.8)	45 (8.4)
Objective Response Rate						
ORR, n (%)	135 (47.7)	134 (47.5)	108 (42.5)	102 (40.3)	243 (45.3)	236 (44.1)
95% CI (%) ¶¶	(41.76, 53.70)	(41.56, 53.52)	(36.36, 48.85)	(34.22, 46.64)	(40.98, 49.57)	(39.85, 48.44)
P value†††	0.4875		0.3104		0.3590	
Disease Control Rate‡‡‡						
DCR, n (%)	232 (82.0)	245 (86.9)	194 (76.4)	192 (75.9)	426 (79.3)	437 (81.7)
95% CI (%) ¶¶	(77.00, 86.28)	(82.37, 90.59)	(70.67, 81.46)	(70.13, 81.03)	(75.65, 82.68)	(78.14, 84.87)
P value†††	0.0569		0.4609		0.1626	
Duration of Response						
Events, n (%)	67 (49.6)	77 (57.5)	66 (61.1)	67 (65.7)	133 (54.7)	144 (61.0)
Median duration, months (95% CI) †	9.00 (6.87, 10.25)	8.05 (6.47, 10.81)	6.14 (5.03, 8.08)	6.08 (4.44, 6.34)	7.72 (6.28, 8.90)	6.47 (6.24, 7.62)
HR (95% CI) ‡	0.876 (0.623, 1.233)		0.758 (0.527, 1.089)		0.819 (0.638, 1.050)	
P value§	0.2218		0.0673		0.0570	

SPOTLIGHT data cutoff: 09 Sep 2022. GLOW data cutoff: 07 Oct 2022
All participants were randomized to 1 of the treatment groups (FAS).
Zolbetuximab: 800 mg/m2 loading dose on Cycle 1, day 1 followed by 600 mg/m2 on subsequent doses.
† Based on Kaplan-Meier estimate.
‡ Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment group.
§ Based on 1-sided log-rank test.

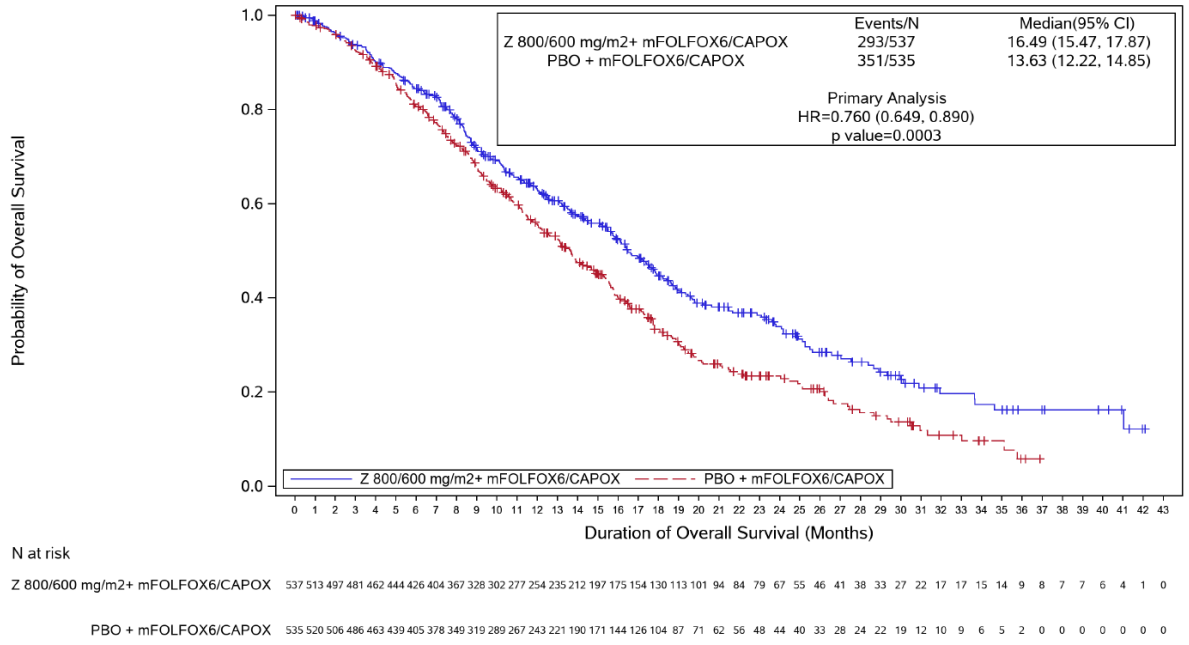
¶ The threshold values of 13 for Physical Functioning and GHS/QoL are based on [Cocks et al, 2012] and the threshold value of 16.7 for OG25-Pain is based on [Norman et al, 2003] and [Sloan et al, 2005].
†† Time to confirmed deterioration = date of first confirmed clinically meaningful deterioration/censored date – randomization date + 1.
‡‡ Based on stratified Cox proportional hazard model with region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables. Assuming proportional hazards, a HR < 1 indicates a reduction in the hazard rate in favor of the treatment group.
§§ The definition of best overall response followed RECIST v1.1. When stable disease (or non-CR/non-progressive disease) was believed to be best response, the assessment should have been at least 8 weeks after randomization. For calculation of percentages, the denominator included the total number of participants in each arm.
¶¶ Using exact method based on binomial distribution (Clopper-Pearson).
††† Based on 1-sided Cochran-Mantel-Haenszel test. Stratification factors were region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis.
‡‡‡ DCR was defined as the proportion of participants who had a best overall response of CR, PR, stable disease or non-CR/non-PD (≥ 8 weeks).

Figure 21: Kaplan-Meier Plot of PFS Assessed by IRC, SPOTLIGHT and GLOW – FAS



Data cutoffs: 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW).
P value is generated from stratified 1-sided log-rank test for the comparison of zolbetuximab plus mFOLFOX6 or CAPOX and placebo plus mFOLFOX6 or CAPOX.
HR with 95% CI is based on stratified Cox proportional hazard model, with region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables.

Figure 22: Kaplan-Meier Plot of OS, SPOTLIGHT and GLOW – FAS



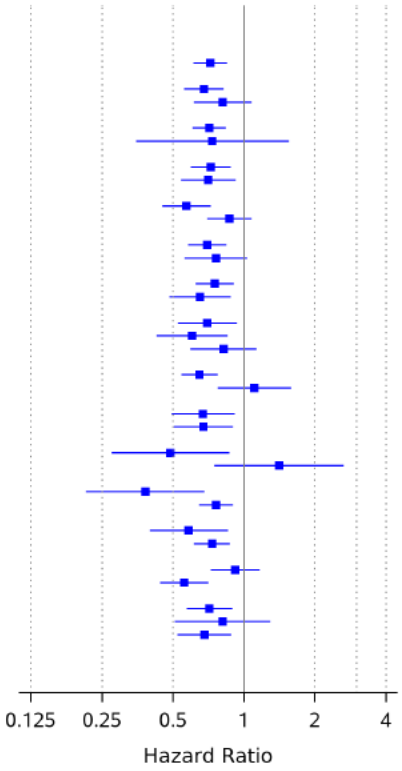
Data cutoffs: 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW).

P value is generated from stratified 1-sided log-rank test for the comparison of zolbetuximab plus mFOLFOX6 or CAPOX and placebo plus mFOLFOX6 or CAPOX.

HR with 95% CI is based on stratified Cox proportional hazard model, with region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables.

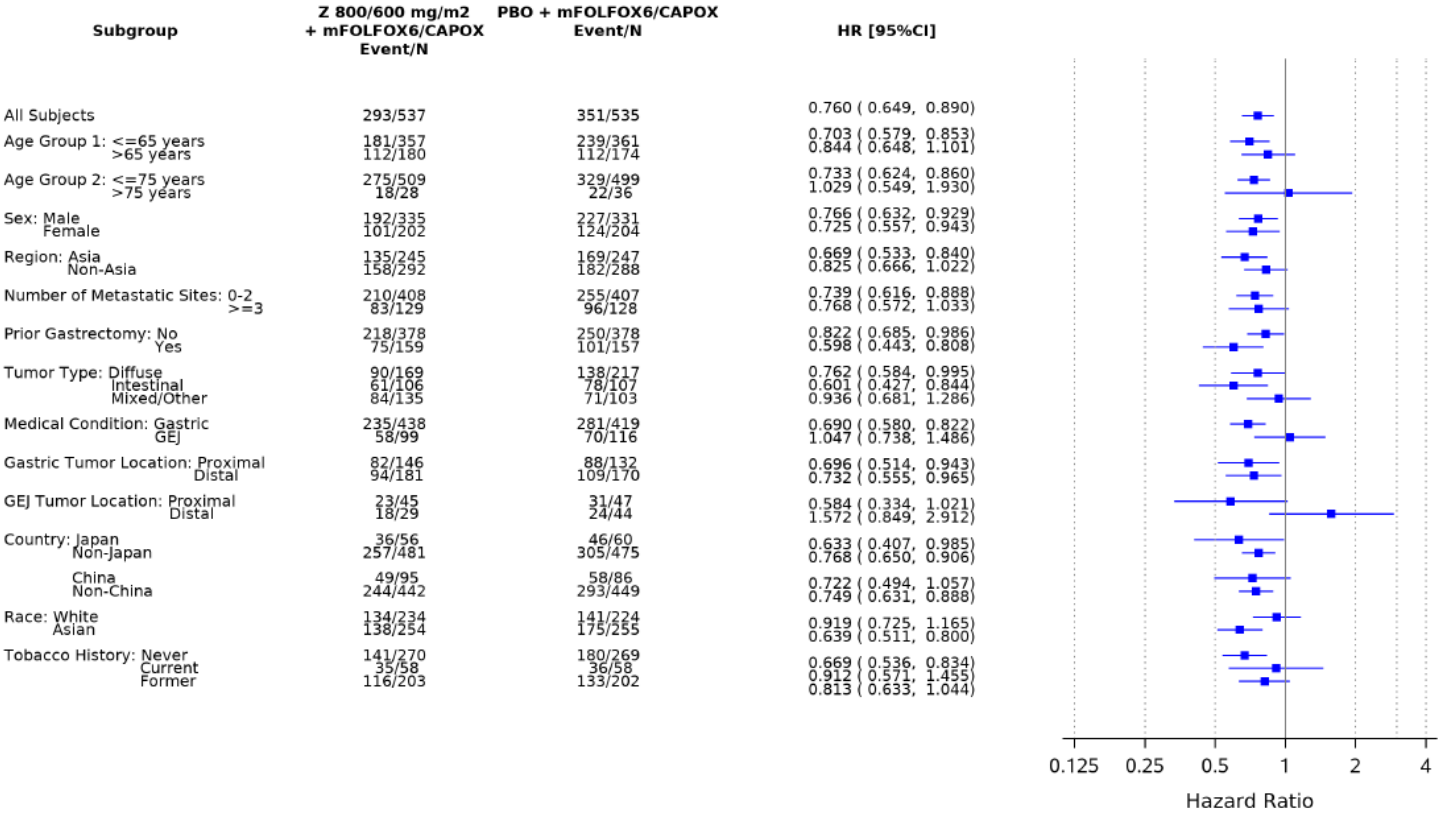
Figure 23: Forest Plot for Subgroup Analysis of PFS Assessed by IRC Across SPOTLIGHT and GLOW – FAS

Subgroup	Z 800/600 mg/m2 + mFOLFOX6/CAPOX Event/N	PBO + mFOLFOX6/CAPOX Event/N	HR [95%CI]
All Subjects	283/537	339/535	0.719 (0.611, 0.846)
Age Group 1: <=65 years	186/357	236/361	0.676 (0.557, 0.820)
>65 years	97/180	103/174	0.812 (0.614, 1.074)
Age Group 2: <=75 years	272/509	319/499	0.713 (0.606, 0.839)
>75 years	11/28	20/36	0.734 (0.348, 1.547)
Sex: Male	187/335	216/331	0.724 (0.594, 0.881)
Female	96/202	123/204	0.705 (0.539, 0.923)
Region: Asia	127/245	156/247	0.569 (0.449, 0.722)
Non-Asia	156/292	183/288	0.867 (0.699, 1.074)
Number of Metastatic Sites: 0-2	204/408	248/407	0.698 (0.579, 0.841)
>=3	79/129	91/128	0.760 (0.562, 1.029)
Prior Gastrectomy: No	203/378	242/378	0.751 (0.623, 0.906)
Yes	80/159	97/157	0.652 (0.484, 0.878)
Tumor Type: Diffuse	78/169	124/217	0.699 (0.525, 0.931)
Intestinal	62/106	72/107	0.603 (0.426, 0.852)
Mixed/Other	77/135	71/103	0.817 (0.591, 1.128)
Medical Condition: Gastric	225/438	275/419	0.648 (0.543, 0.774)
GEJ	58/99	64/116	1.107 (0.774, 1.583)
Gastric Tumor Location: Proximal	80/146	84/132	0.671 (0.492, 0.915)
Distal	85/181	105/170	0.672 (0.504, 0.896)
GEJ Tumor Location: Proximal	23/45	31/47	0.487 (0.275, 0.865)
Distal	16/29	25/44	1.406 (0.748, 2.644)
Country: Japan	19/56	33/60	0.381 (0.214, 0.680)
Non-Japan	264/481	306/475	0.761 (0.645, 0.899)
China	51/95	58/86	0.583 (0.398, 0.855)
Non-China	232/442	281/449	0.732 (0.614, 0.872)
Race: White	129/234	140/224	0.917 (0.721, 1.165)
Asian	130/254	160/255	0.558 (0.441, 0.705)
Tobacco History: Never	148/270	169/269	0.714 (0.571, 0.892)
Current	35/58	38/58	0.810 (0.509, 1.290)
Former	99/203	131/202	0.680 (0.522, 0.884)



Data cutoffs: 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW).
In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. The HR reported for all participants was based on stratified analysis.

Figure 24: Forest Plot for Subgroup Analysis of Overall Survival Across SPOTLIGHT and GLOW – FAS



Data cutoffs: 09 Sep 2022 (SPOTLIGHT); 07 Oct 2022 (GLOW).

In each subgroup, the HR was estimated using unstratified Cox proportional hazard model with treatment as the only explanatory variable. The HR reported for all participants was based on stratified analysis.

Table 81: Subgroup analysis of ORR, ICR, unconfirmed responses (from Table 8.4.2.2.1)

		SPOTLIGHT/GLOW					
		Z 800/600 mg/m2 + mFOLFOX6/CAPOX			PBO + mFOLFOX6/CAPOX		Absolute Difference [2]
Parameter	Value	N	n (ORR) [1]	95% CI	N	n (ORR) [1]	95% CI	95% CI
All	-	537	243 (45.3%)	(40.98%, 49.57%)	535	236 (44.1%)	(39.85%, 48.44%)	1.1% (-4.85%, 7.14%)
Age Group 1	<=65 years	357	156 (43.7%)	(38.48%, 49.02%)	361	148 (41.0%)	(35.88%, 46.27%)	2.7% (-4.61%, 9.96%)
	>65 years	180	87 (48.3%)	(40.84%, 55.89%)	174	88 (50.6%)	(42.90%, 58.22%)	-2.2% (-12.71%, 8.27%)
Age Group 2	<=75 years	509	232 (45.6%)	(41.19%, 50.02%)	499	212 (42.5%)	(38.10%, 46.96%)	3.1% (-3.08%, 9.27%)
	>75 years	28	11 (39.3%)	(21.50%, 59.42%)	36	24 (66.7%)	(49.03%, 81.44%)	-27.4% (-49.98%, -1.93%)
Sex	Male	335	163 (48.7%)	(43.19%, 54.15%)	331	155 (46.8%)	(41.35%, 52.36%)	1.8% (-5.82%, 9.50%)
	Female	202	80 (39.6%)	(32.81%, 46.71%)	204	81 (39.7%)	(32.94%, 46.77%)	-0.1% (-9.69%, 9.47%)
Region	Asia	245	101 (41.2%)	(35.00%, 47.67%)	247	99 (40.1%)	(33.92%, 46.48%)	1.1% (-7.61%, 9.85%)
	Non-Asia	292	142 (48.6%)	(42.77%, 54.52%)	288	137 (47.6%)	(41.68%, 53.51%)	1.1% (-7.14%, 9.28%)
Number of Metastatic Sites	0-2	408	175 (42.9%)	(38.03%, 47.85%)	407	175 (43.0%)	(38.13%, 47.97%)	-0.1% (-6.94%, 6.74%)
	>=3	129	68 (52.7%)	(43.74%, 61.56%)	128	61 (47.7%)	(38.76%, 56.66%)	5.1% (-7.43%, 17.42%)
Prior Gastrectomy	No	378	171 (45.2%)	(40.14%, 50.41%)	378	179 (47.4%)	(42.23%, 52.52%)	-2.1% (-9.28%, 5.07%)
	Yes	159	72 (45.3%)	(37.39%, 53.36%)	157	57 (36.3%)	(28.79%, 44.35%)	9.0% (-1.94%, 19.80%)
Tumor Type	Diffuse	169	69 (40.8%)	(33.34%, 48.64%)	217	91 (41.9%)	(35.29%, 48.80%)	-1.1% (-11.01%, 8.95%)
	Intestinal	106	52 (49.1%)	(39.22%, 58.95%)	107	52 (48.6%)	(38.82%, 58.46%)	0.5% (-13.28%, 14.09%)
	Mixed/Other	135	65 (48.1%)	(39.47%, 56.91%)	103	50 (48.5%)	(38.58%, 58.60%)	-0.4% (-13.26%, 12.43%)
Medical Condition	Gastric	438	196 (44.7%)	(40.03%, 49.54%)	419	176 (42.0%)	(37.23%, 46.89%)	2.7% (-3.98%, 9.40%)
	GEJ	99	47 (47.5%)	(37.34%, 57.76%)	116	60 (51.7%)	(42.26%, 61.10%)	-4.2% (-17.66%, 9.21%)
Gastric Tumor Location	Proximal	146	67 (45.9%)	(37.62%, 54.33%)	132	57 (43.2%)	(34.59%, 52.08%)	2.7% (-9.10%, 14.50%)
	Distal	181	77 (42.5%)	(35.24%, 50.09%)	170	75 (44.1%)	(36.52%, 51.92%)	-1.6% (-12.01%, 8.88%)
GEJ Tumor Location	Proximal	45	22 (48.9%)	(33.70%, 64.23%)	47	21 (44.7%)	(30.17%, 59.88%)	4.2% (-16.83%, 24.65%)
	Distal	29	15 (51.7%)	(32.53%, 70.55%)	44	27 (61.4%)	(45.50%, 75.64%)	-9.6% (-32.83%, 14.30%)
Country	Japan	56	28 (50.0%)	(36.34%, 63.66%)	60	27 (45.0%)	(32.12%, 58.39%)	5.0% (-13.47%, 23.14%)
	Non-Japan	481	215 (44.7%)	(40.20%, 49.27%)	475	209 (44.0%)	(39.48%, 48.59%)	0.7% (-5.63%, 7.07%)
	China	95	38 (40.0%)	(30.08%, 50.56%)	86	35 (40.7%)	(30.22%, 51.83%)	-0.7% (-15.29%, 13.75%)
	Non-China	442	205 (46.4%)	(41.66%, 51.15%)	449	201 (44.8%)	(40.10%, 49.50%)	1.6% (-5.00%, 8.17%)
Race	White	234	115 (49.1%)	(42.57%, 55.74%)	224	107 (47.8%)	(41.07%, 54.52%)	1.4% (-7.87%, 10.56%)
	Asian	254	106 (41.7%)	(35.60%, 48.06%)	255	100 (39.2%)	(33.18%, 45.50%)	2.5% (-6.08%, 11.07%)
Tobacco History	Never	270	125 (46.3%)	(40.23%, 52.44%)	269	103 (38.3%)	(32.45%, 44.39%)	8.0% (-0.40%, 16.35%)
	Current	58	27 (46.6%)	(33.34%, 60.13%)	58	32 (55.2%)	(41.54%, 68.26%)	-8.6% (-27.18%, 10.39%)
	Former	203	88 (43.3%)	(36.43%, 50.47%)	202	99 (49.0%)	(41.93%, 56.12%)	-5.7% (-15.41%, 4.21%)

Measurable vs non measurable disease

Table 82: Overview of PFS and OS in participants with measurable and non measurable disease

	Measurable disease		No measurable disease	
	Integrated Efficacy Analysis SPOTLIGHT and GLOW		Integrated Efficacy Analysis SPOTLIGHT and GLOW	
Parameter	Zolbetuximab plus mFOLFOX6 or CAPOX (n = 406)	Placebo plus mFOLFOX6 or CAPOX (n = 416)	Zolbetuximab plus mFOLFOX6 or CAPOX (n = 131)	Placebo plus mFOLFOX6 or CAPOX (n = 119)
PFS (Assessed by IRC)				
Median duration, months (95% CI)	8.3 (8.1, 8.5)	7.8 (6.5, 8.3)	18.1 (15.5, 23.3)	10.3 (8.2, 13.0)
HR (95% CI)	0.81 (0.68, 0.97)		0.48 (0.31, 0.73)	
Overall Survival				
Median duration, months (95% CI)	14.5 (12.7, 16.2)	13.2 (11.5, 14.3)	25.3 (18.6, NE)	15.6 (12.3, 18.1)
HR (95% CI)	0.86 (0.72, 1.02)		0.52 (0.35, 0.78)	

Efficacy by tumour status (metastatic vs locally advanced disease)

Table 83: Summary of PFS and OS by tumour status for SPOTLIGHT and GLOW (Assessor's table from response to D120 LoQ Q163)

	Metastatic disease		Locally advanced disease	
	SPOTLIGHT		SPOTLIGHT	
Parameter	Zolbetuximab plus mFOLFOX6 (n = 239)	Placebo plus mFOLFOX6 (n = 238)	Zolbetuximab plus mFOLFOX6 (n = 44)	Placebo plus mFOLFOX6 (n = 44)
PFS (Assessed by IRC)				
Median duration, months (95% CI)	10.3 (8.5, 12.5)	8.6 (8.2, 10.3)	12.4 (10.4, NE)	10.2 (6.0, 16.0)
HR (95% CI)	0.77 (0.60, 0.98)		0.76 (0.40, 1.44)	
Overall Survival				
Median duration, months (95% CI)	17.8 (15.7, 21.5)	15.6 (13.7, 17.3)	21.5 (16.4, 25.3)	10.6 (8.9, 29.3)
HR (95% CI)	0.79 (0.62, 1.0)		0.57 (0.30, 1.08)	
	GLOW		GLOW	
	Zolbetuximab plus CAPOX (n = 222)	Placebo plus CAPOX (n =222)	Zolbetuximab plus CAPOX (n = 32)	Placebo plus CAPOX (n = 31)
PFS (Assessed by IRC)				
Median duration, months (95% CI)	8.2 (7.8, 8.8)	7.3 (6.1, 8.2)	8.5 (5.4, 12.0)	6.3 (4.2, 8.1)
HR (95% CI)	0.70 (0.54, 0.89)		0.72 (0.36, 1.45)	
Overall Survival				
Median duration, months (95% CI)	14.4 (12.1, 16.5)	12.1 (10.3, 13.7)	16.4 (10.2, 34.6)	12.6 (7.7, 21.5)
HR (95% CI)	0.78 (0.62, 0.99)		0.52 (0.21, 1.25)	

Post-hoc exploratory analyses to evaluate the discrepant results for OS/PFS vs ORR/DCR:

- Tumour shrinkage

Table 84: Best % Change from Baseline in Sum of Diameters for Target Lesions by IRC for SPOTLIGHT, GLOW and SPOTLIGHT/GLOW

Analysis Visit	Statistics	SPOTLIGHT		GLOW		SPOTLIGHT/GLOW	
		Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Baseline	n	210	208	195	201	405	409
Best % Change Post Baseline Visit	n	185	195	161	177	346	372
	Mean	-50.0	-41.1	-42.2	-34.7	-46.4	-38.1
	Standard deviation	31.2	33.8	35.7	30.9	33.5	32.6
	Median	-51.7	-45.6	-44.1	-33.6	-47.9	-38.4

Best % change is the minimum value of change from baseline from all the post-baseline visit.

- Time to progression (TTP) by response status

Table 85: Median time to progression (TTP) by best overall response (BOR) (Assessor's table from D120 response to Q168)

	Integrated Efficacy Analysis SPOTLIGHT and GLOW	
	Zolbetuximab plus mFOLFOX6 or CAPOX	Placebo plus mFOLFOX6 or CAPOX
BOR = PR		
TTP; Median, months	12.4	10.5
HR (95% CI)	0.86 (0.63, 1.19)	
BOR = SD		
TTP; Median, months	8.51	6.37
HR (95% CI)	0.74 (0.46, 1.19)	
BOR = SD or non-CR/non-PD		
TTP; Median, months	18.1	10.4
HR (95% CI)	0.6 (0.41, 0.87)	

Ancillary analyses to explore efficacy by subgroups of Caucasian/Asian and GC/GEJ (proximal/distal)

Efficacy results in subgroups

Table 86: Caucasian, Asian, GC and GEJ Subgroup Analyses of PFS (by IRC Assessment) and OS for Integrated SPOTLIGHT/GLOW: Zolbetuximab/Placebo (FAS)

Parameter		PFS		OS	
		Arm A	Arm B	Arm A	Arm B
Caucasian Subgroup	N	234	224	234	224
	Median (Months)	8.51	8.67	15.34	14.69
	HR (95% CI)	**0.923** (0.725, 1.176)		**0.936** (0.737, 1.187)	
Asian Subgroup	N	254	255	254	255
	Median (Months)	10.41	7.20	17.81	13.01
	HR (95% CI)	0.548 (0.431, 0.696)		0.645 (0.514, 0.810)	
GC Subgroup	N	438	419	438	419
	Median (Months)	9.79	7.85	16.99	13.17
	HR (95% CI)	0.645 (0.539, 0.773)		0.701 (0.589, 0.836)	
GEJ Subgroup	N	99	116	99	116
	Median (Months)	8.34	9.23	15.51	15.80
	HR (95% CI)	**1.011** (0.696, 1.470)		**1.114** (0.770, 1.610)	
GEJ Proximal Subgroup	N	45	47	45	47
	Median (Months)	10.28	7.36	17.54	15.64
	HR (95% CI)	0.487 (0.275, 0.865)		0.584 (0.334, 1.021)	
GEJ Distal Subgroup	N	29	44	29	44
	Median (Months)	8.71	10.58	13.08	15.84
	HR (95% CI)	**1.406** (0.748, 2.644)		**1.572** (0.849, 2.912)	
Overall Population	N	537	535	537	535
	Median (Months)	8.94	8.15	16.49	13.63
	HR (95% CI)	0.719 (0.611, 0.846)		0.760 (0.649, 0.890)	

Arm A = Zolbetuximab + mFOLFOX6/CAPOX, Arm B = Placebo + mFOLFOX6/CAPOX
The HR with 95% CI is based on stratified Cox proportional hazard model, with region, number of metastatic sites and prior gastrectomy as the explanatory variables.

Table 87: Analysis by Regional Subgroups and Overall Population of PFS (by IRC Ass.) and OS for Integrated SPOTLIGHT/GLOW: Zolbetuximab/Placebo

Parameter		PFS		OS	
		Arm A	Arm B	Arm A	Arm B
European Subgroup [1]	N	**220**	**208**	**220**	**208**
	Median (Months)	8.77	8.67	15.87	13.96
	HR (95% CI)	**0.854** (0.662, 1.103)		**0.867** (0.672, 1.118)	
Asia Pacific Subgroup	N	247	252	247	252
	Median (Months)	10.41	7.20	17.58	13.14
	HR (95% CI)	**0.556** (0.437, 0.707)		**0.666** (0.530, 0.836)	
North America Subgroup	N	36	48	36	48
	Median (Months)	11.04	8.57	16.99	15.64
	HR (95% CI)	**0.869** (0.477, 1.584)		**0.716** (0.401, 1.277)	
South America Subgroup	N	34	27	34	27
	Median (Months)	6.97	7.59	7.72	8.48
	HR (95% CI)	**1.577** (0.791, 3.141)		**0.992** (0.503, 1.957)	
Overall Population	N	537	535	537	535
	Median (Months)	8.94	8.15	16.49	13.63
	HR (95% CI)	**0.710** (0.604, 0.834)		**0.752** (0.643, 0.880)	

[1] European Subgroup also contains 2 participants from Israel (SPOTLIGHT) and 37 from Turkey (GLOW).

Table 88: Subgroup Analyses by Race and Medical Condition for PFS (by IRF) and OS for Integrated SPOTLIGHT/GLOW– Excerpt from D120 responses Table 24

Parameter	Integrated SPOTLIGHT/GLOW							
	Caucasian-GEJ		Asian-GEJ		Caucasian-GC		Asian-GC	
	Arm A N=56	Arm B N=72	Arm A N=27	Arm B N=29	Arm A N=178	Arm B N=152	Arm A N=227	Arm B N=226
PFS								
Median Duration (Months)	8.71	10.38	8.11	7.95	8.44	8.21	10.58	6.57
HR (95% CI) Strat.	1.114 (0.689, 1.800)		0.897 (0.411, 1.958)		0.821 (0.617, 1.093)		0.527 (0.408, 0.679)	
OS								
Median Duration (Months)	14.39	15.84	17.71	11.53	15.87	13.70	17.84	13.11
HR (95% CI) Strat.	1.416 (0.883, 2.269)		0.796 (0.366, 1.730)		0.816 (0.616, 1.082)		0.653 (0.513, 0.831)	

Biomarker expression in subgroups

- By race

Table 89: Number (%) of Screened Participants in SPOTLIGHT and GLOW by CLDN18 Staining Categories

CLDN18 staining category	SPOTLIGHT All [1] N=2403	SPOTLIGHT Caucasian N=1108	SPOTLIGHT Asian N=816	GLOW All [1] N=2104	GLOW Caucasian N=719	GLOW Asian N=1333
Negative	26.6 (n=639)	25.9 (n=287)	27.8 (n=227)	26.8 (n=563)	27.4 (n=197)	26.2 (n=349)
< 50%	24.3 (n=585)	21.1 (n=234)	27.5 (n=224)	24.6 (n=517)	21.1 (n=152)	26.5 (n=353)
50 – 74%	10.7 (n=257)	9.9 (n=110)	9.4 (n=77)	10.3 (n=216)	10.4 (n=75)	10.2 (n=136)
≥ 75%	38.4 (n=922)	43.1 (n=477)	35.3 (n=288)	38.4 (n=808)	41.0 (n=295)	37.1 (n=495)

[1] Number of unique subjects with valid CDLN18.2 IHC results.

- By medical condition (GC/GEJ)

Table 90: Prevalence Rates of CLDN18.2 Negative Status and CLDN18.2 Positive Prevalence in GC and GEJ Participants in SPOTLIGHT and GLOW

CLDN18 staining category	SPOTLIGHT All [1] N=2403	SPOTLIGHT GC N=1677	SPOTLIGHT GEJ N=591	GLOW All [1] N=2104	GLOW GC N=1680	GLOW GEJ N=310
Negative	26.6% (n=639)	25.6% (n=429)	27.7% (n=164)	26.8% (n=563)	26.0% (n=436)	27.1% (n=84)
< 50%	24.3% (n=585)	24.0% (n=403)	24.7% (n=146)	24.6% (n=517)	24.6% (n=413)	22.6% (n=70)
50% – 74%	10.7% (n=257)	10.3% (n=172)	10.8% (n=64)	10.3% (n=216)	9.7% (n=163)	11.3% (n=35)
≥ 75%	38.4% (n=922)	40.1% (n=673)	36.7% (n=217)	38.4% (n=808)	39.8% (n=668)	39.0% (n=121)

Baseline characteristics in subgroups

- By race

Table 91: Selected Baseline Demographic and Disease Characteristics in Caucasian and Asian Subgroups –

Parameter	Integrated SPOTLIGHT/GLOW				Overall Population	
	Caucasian		Asian			
	Arm A N=234	Arm B N=224	Arm A N=254	Arm B N=255	Arm A N=537	Arm B N= 535
Sex, Male (%)	61.5	64.7	64.2	60.8	62.4	61.9
Mean Age (Years)	60.3	58.2	58.3	57.4	59.2	57.8
ECOG Status at Baseline						
0 (%)	45.0	40.8	41.5	43.6	43.8	42.2
1 (%)	55.0	59.2	58.5	56.4	56.2	57.8
Mean Weight (kg)	67.91	70.54	58.12	56.09	63.20	62.94
Mean BMI (kg/m^2)	24.16	24.77	21.70	20.99	23.00	22.80
Mean BSA (m^2)	1.77	1.81	1.62	1.60	1.70	1.70
Tobacco History						
Never (%)	47.4	48.2	50.8	53.8	50.8	50.9
Current (%)	13.9	10.0	9.1	12.3	10.9	11.0
Former (%)	38.7	41.8	40.2	34.0	38.2	38.2
GEJ (%)	23.9	32.1	10.6	11.4	18.4	21.7
Number of Metastatic Sites						
0-2 (%)	72.2	72.3	79.1	78.0	76.0	76.1
≥ 3 (%)	27.8	27.7	20.9	22.0	24.0	23.9
Prior Gastrectomy (%)	26.1	25.4	35.0	35.7	29.6	29.3
Tumor Type						
Diffuse (%)	24.9	33.8	39.5	46.2	31.6	40.9
Intestinal (%)	19.3	17.6	18.2	20.6	19.8	20.2
Peritoneal Metastasis (%)	34.6	32.1	36.2	35.7	35.8	34.0
Liver Metastasis (%)	30.8	28.1	19.3	20.4	25.1	24.7

- By medical condition (GC/GEJ)

Table 92: Selected Baseline Demographic and Disease Characteristics in GC and GEJ Subgroups for Integrated SPOTLIGHT/GLOW

Parameter	Integrated SPOTLIGHT/GLOW				Overall Population	
	GC		GEJ			
	Arm A N=438	Arm B N=419	Arm A N=99	Arm B N=116	Arm A N=537	Arm B N=535
Sex, Male (%)	58.2	56.6	80.8	81.0	62.4	61.9
Race, Caucasian (%)	41.8	38.2	64.4	69.9	45.6	44.7
Race, Asian (%)	53.3	56.8	31.0	28.2	49.5	50.9
Mean Age (Years)	58.5	56.9	62.2	60.8	59.2	57.8
ECOG Status 0 at Baseline (%)	44.0	40.6	42.9	48.2	43.8	42.2
ECOG Status 1 at Baseline (%)	56.0	59.4	56.1	51.8	56.2	57.8
Mean Weight (kg)	62.20	60.52	67.67	71.72	63.20	62.94
Mean BMI (kg/m^2)	22.90	22.33	23.43	24.51	23.00	22.80
Mean BSA (m^2)	1.68	1.66	1.78	1.83	1.70	1.70
Tobacco History Never (%)	52.8	53.8	42.3	40.5	50.8	50.9
Tobacco History Current (%)	10.8	9.9	11.3	14.7	10.9	11.0
Tobacco History Former (%)	36.4	36.3	46.4	44.8	38.2	38.2
Number of Metastatic Sites 0-2 (%)	76.9	77.1	71.7	72.4	76.0	76.1
Number of Metastatic Sites ≥ 3 (%)	23.1	22.9	28.3	27.6	24.0	23.9
Prior Gastrectomy (%)	31.3	31.0	22.2	23.3	29.6	29.3
Peritoneal Metastasis (%)	39.0	39.9	21.2	12.9	35.8	34.0
Liver Metastasis (%)	23.1	22.2	34.3	33.6	25.1	24.7

Exposure to Zolbetuximab/Oxaliplatin by race and medical condition

Table 93: Comparison of Study Drug Treatment in Caucasian and Asian Subgroups in SPOTLIGHT and GLOW and the Overall Population (SAS)

	Caucasian		Asian		Overall Population	
Parameter	**Arm A**	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**
SPOTLIGHT						
Zolbetuximab/Placebo Exposure						
N	138	134	95	94	279	278
Duration of Exposure (Days)						
Mean	232.7	250.9	338.9	228.4	260.6	237.0
Median	176.0	211.5	253.0	168.0	190.0	195.0
Cumulative Actual Dose (mg/m²)						
Mean	6584.614	7291.009	9276.787	6525.776	7308.702	6858.815
Median	5214.709	6216.000	7400.000	5000.000	5600.000	5638.751
Relative Dose Intensity n (%)						
> 80%	113 (81.9)	130 (97.0)	90 (94.7)	94 (100.0)	239 (85.7)	274 (98.6)
Infusion with Interruption						
n (%)	98 (71.0)	13 (9.7)	39 (41.1)	2 (2.1)	166 (59.5)	15 (5.4)
Prematurely Discontinued Infusion						
n (%)	34 (24.6)	0	7 (7.4)	0	49 (17.6)	0
Time to First Dose Modification (Days)						
N	109	53	58	16	202	86
Mean	25.2	113.0	79.9	106.7	142	112.3
Median	1.0	92.0	24.5	84.0	1.9	92.0
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days) [1]						
N	137	134	93	94	274	278
Mean	123.2	129.5	150.2	130.3	131.3	130.0
Median	142.0	152.5	162.0	137.5	150.0	148.0
GLOW						
Zolbetuximab/Placebo Exposure						
N	94	88	158	156	254	249
Duration of Exposure (Days)						
N	93	89	157	156	253	249
Mean	175.3	198.4	208.1	164.2	194.8	176.7
Median	112.0	175.0	148.0	133.0	134.0	148.0
Cumulative Actual Dose (mg/m²)						
Mean	5186.362	5972.141	6058.233	4909.477	5706.338	5294.084
Median	3800.000	5300.000	4400.000	4400.000	3832.632	4400.000
Relative Dose Intensity (%)						
> 80%	82 (87.2)	87 (98.9)	154 (97.5)	156 (100.0)	238 (93.7)	248 (99.6)
Infusion with Interruption						
n (%)	49 (52.1)	5 (5.7)	57 (36.1)	4 (2.6)	108 (42.5)	10 (4.0)
Prematurely Discontinued Infusion						
n (%)	14 (14.9)	1 (1.1)	12 (7.6)	2 (1.3)	27 (10.6)	3 (1.2)
Time to First Dose Modification (Days)						
N	62	34	75	28	139	64
Mean	18.0	98.4	43.8	102.4	31.8	98.5
Median	1.0	71.0	1.0	92.0	1.0	79.0
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days) [1]						
N	91	89	156	156	250	249
Mean	110.1	117.8	110.4	107.0	110.2	110.4
Median	121.0	134.0	128.0	113.0	123.5	118.0

[1] Duration is defined as (date of last dose) – (date of first dose) + 1.

Table 98: Comparison of Study Drug Treatment in Caucasian-GEJ, Asian-GEJ, Caucasian-GC, and Asian-GC Subgroups (SAS) in Integrated SPOTLIGHT/GLOW

Parameter	Integrated SPOTLIGHT/GLOW							
	Caucasian-GEJ		Asian-GEJ		Caucasian-GC		Asian-GC	
	Arm A N=56	Arm B N=71	Arm A N=27	Arm B N=28	Arm A N=176	Arm B N=151	Arm A N=226	Arm B N=222
Duration of Zolbetuximab/Placebo Exposure (Days)								
N	56	71	27	28	176	151	225	222
Mean	187.2	256.7	218.2	139.3	216.4	217.9	262.1	194.6
Median	141.0	239.0	174.0	126.0	169.0	176.0	190.0	156.0
Cumulative Actual Dose (mg/m²)								
Mean	5590.777	7370.403	6308.103	4222.762	6154.041	6485.067	7387.194	5680.468
Median	4400.000	6800.000	5000.000	4100.000	4400.000	5600.000	5600.000	4400.553
Relative Dose Intensity n (%)								
> 80%	48 (85.7)	69 (97.2)	26 (96.3)	28 (100.0)	147 (83.5)	148 (98.0)	218 (96.5)	222 (100.0)
Infusion with Interruption								
n (%)	36 (64.3)	6 (8.5)	10 (37.0)	0	111 (63.1)	12 (7.9)	86 (38.1)	6 (2.7)
Prematurely Discontinued Infusion								
n (%)	11 (19.6)	0	2 (7.4)	0	37 (21.0)	1 (0.7)	17 (7.5)	2 (0.9)
Time to First Dose Modification (Days)								
N	42	31	15	4	129	56	118	40
Mean	23.9	95.2	54.4	104.3	22.2	114.1	60.2	103.9
Median	1.0	71.0	26.0	112.5	1.0	85.0	1.0	90.5
Duration of Oxaliplatin Exposure (Days) [1]								
N	55	71	27	28	174	151	222	222
Mean	109.7	138.2	117.4	110.3	120.7	118.5	126.2	116.5
Median	120.0	155.0	134.0	112.0	141.5	139.0	148.0	127.0

[1] Duration is defined as (date of last dose) – (date of first dose) + 1.

Table 94: Comparison of Study Drug Treatment in GC and GEJ Subgroups and the Overall Population in SPOTLIGHT and GLOW (SAS)

Parameter	GC		GEJ		Overall	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
SPOTLIGHT						
Zolbetuximab/Placebo Exposure						
n	216	207	63	71	279	278
Duration of Exposure (Days)						
Mean	275.9	238.8	208.2	231.7	260.6	237.0
Median	208.5	190.0	174.0	211.0	190.0	195.0
Cumulative Actual Dose (mg/m²)						
Mean	7664.838	6915.855	6087.666	6692.517	7308.702	6858.815
Median	6044.046	5600.000	5000.000	6200.000	5600.000	5638.751
Relative Dose Intensity (n [%])						
> 80%	185 (85.6)	205 (99.0)	54 (85.7)	69 (97.2)	239 (85.7)	274 (98.6)
Infusion with Interruption						
n (%)	126 (58.3)	10 (4.8)	40 (63.5)	5 (7.0)	166 (59.5)	15 (5.4)
Prematurely Discontinued Infusion						
n (%)	38 (17.6)	0	11 (17.5)	0	49 (17.6)	0
Time to First Dose Modification (Days) [1]						

Parameter	GC		GEJ		Overall	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Mean	41.9	120.7	35.0	92.9	NR	NR
Median	1.0	103.5	1.0	49.0	NR	NR
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days) [2]						
n	212	207	62	71	274	278
Mean	135.7	129.6	116.0	131.1	131.3	130.0
Median	155.0	144.0	123.0	155.0	150.0	148.0
GLOW						
Zolbetuximab/Placebo Exposure						
n	218	207	36	42	254	249
Duration of Exposure (Days)						
n	217	207	35	43	253	249
Mean	202.1	176.0	151.1	179.9	194.8	176.7
Median	138.0	140.0	103.0	155.0	134.0	148.0
Cumulative Actual Dose (mg/m^2)						
Mean	5880.386	5263.655	4657.219	5444.054	5706.338	5294.084
Median	4400.000	4400.000	3483.500	4670.457	3832.632	4400.000
Relative Dose Intensity (%)						
> 80%	205 (94.0)	206 (99.5)	33 (91.7)	42 (100.0)	238 (93.7)	248 (99.6)
Infusion with Interruption						
n (%)	90 (41.3)	9 (4.3)	18 (50.0)	1 (2.4)	108 (42.5)	10 (4.0)
Prematurely Discontinued Infusion						
n (%)	23 (10.6)	3 (1.4)	4 (11.1)	0	27 (10.6)	3 (1.2)
Time to First Dose Modification (Days) [1]						
Mean	32.6	99.7	28.2	93.4	NR	NR
Median	1.0	79.0	1.0	85.0	NR	NR
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days) [2]						
n	214	207	35	43	250	249
Mean	112.0	109.7	98.2	114.3	110.2	110.4
Median	128.0	117.0	112.0	128.0	123.5	118.0

Table 100: Comparison of Study Drug Treatment in GEJ Proximal vs GEJ Distal Subgroups

Parameter	GEJ Proximal		GEJ Distal		Overall Population	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
SPOTLIGHT						
Zolbetuximab/Placebo Exposure						
n	30	26	19	30	279	278
Duration of Exposure (Days)						
Mean	243.5	168.0	205.3	279.4	260.6	237.0
Median	187.0	151.5	162.0	254.5	190.0	195.0
Cumulative Actual Dose (mg/m²)						
Mean	7028.692	5071.595	5973.920	7986.967	7308.702	6858.815
Median	5600.000	4390.000	5000.000	7400.000	5600.000	5638.751
Relative Dose Intensity (%)						
> 80%	27 (90.0)	25 (96.2)	15 (78.9)	30 (100.0)	239 (85.7)	274 (98.6)
Infusion with Interruption						
n (%)	20 (66.7)	1 (3.8)	11 (57.9)	3 (10.0)	166 (59.5)	15 (5.4)
Prematurely Discontinued Infusion						
n (%)	5 (16.7)	0	4 (21.1)	0	49 (17.6)	0
Time to First Dose Modification (Days)						
Mean	29.0	63.3	25.2	112.8	NR	NR
Median	1.0	40.0	1.0	104.0	NR	NR
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days)						
n	30	26	19	30	274	278
Mean	124.4	113.9	117.2	150.0	131.3	130.0
Median	134.0	115.5	119.0	162.0	150.0	148.0
GLOW						
Zolbetuximab/Placebo Exposure						
n	16	19	10	13	254	249
Duration of Exposure (Days)						
n	15	19	10	13	253	249
Mean	169.0	132.1	104.1	250.1	194.8	176.7
Median	113.0	109.0	77.0	183.0	134.0	148.0
Cumulative Actual Dose (mg/m²)						
Mean	5147.540	4052.393	3272.302	7362.677	5706.338	5294.084
Median	4400.000	3200.000	2600.000	5600.000	3832.632	4400.000
Relative Dose Intensity (%)						
> 80%	16 (100.0)	19 (100.0)	8 (80.0)	13 (100.0)	238 (93.7)	248 (99.6)
Infusion with Interruption						
n (%)	9 (56.3)	0	6 (60.0)	1 (7.7)	108 (42.5)	10 (4.0)
Prematurely Discontinued Infusion						
n (%)	0	0	3 (30.0)	0	27 (10.6)	3 (1.2)
Time to First Dose Modification (Days)						
Mean	23.4	75.5	33.0	111.3	NR	NR
Median	1.0	71.0	1.0	129.5	NR	NR

Parameter	GEJ Proximal		GEJ Distal		Overall Population	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Oxaliplatin Exposure						
Duration of Oxaliplatin Exposure (Days)						
n	15	20	10	13	250	249
Mean	102.0	105.8	86.0	139.6	110.2	110.4
Median	113.0	109.0	83.5	149.0	123.5	118.0

End-of-treatment Reasons and Toxicity (AEs leading to discontinuations)

- By race

Table 95: End-of-Treatment Reasons in Caucasian and Asian Adenocarcinoma Subgroups – Discontinuation of Zolbetuximab/Placebo (FAS)

Parameter Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Caucasian						
n	140	134	94	90	234	224
Discontinuation						
No	27 (19.3)	26 (19.4)	11 (11.7)	10 (11.1)	38 (16.2)	36 (16.1)
Yes	113 (80.7)	108 (80.6)	83 (88.3)	80 (88.9)	196 (83.8)	188 (83.9)
Primary Study Drug Treatment Status						
Adverse Event	24 (17.1)	5 (3.7)	21 (22.3)	4 (4.4)	45 (19.2)	9 (4.0)
Death	8 (5.7)	11 (8.2)	10 (10.6)	9 (10.0)	18 (7.7)	20 (8.9)
Lost to Follow-Up	1 (0.7)	0	1 (1.1)	0	2 (0.9)	0
Progressive Disease	61 (43.6)	84 (62.7)	32 (34.0)	61 (67.8)	93 (39.7)	145 (64.7)
Protocol Deviation	1 (0.7)	0	0	0	1 (0.4)	0
Withdrawal by Participant	11 (7.9)	4 (3.0)	9 (9.6)	5 (5.6)	20 (8.5)	9 (4.0)
Other	7 (5.0)	4 (3.0)	10 (10.6)	1 (1.1)	17 (7.3)	5 (2.2)
Asian						
n	96	97	158	158	254	255
Discontinuation						
No	12 (12.5)	8 (8.2)	19 (12.0)	8 (5.1)	31 (12.2)	16 (6.3)
Yes	84 (87.5)	89 (91.8)	139 (88.0)	150 (94.9)	223 (87.8)	239 (93.7)
Primary Study Drug Treatment Status						
Adverse Event	10 (10.4)	5 (5.2)	13 (8.2)	11 (7.0)	23 (9.1)	16 (6.3)
Death	1 (1.0)	1 (1.0)	14 (8.9)	12 (7.6)	15 (5.9)	13 (5.1)
Lost to Follow-Up	0	0	0	1 (0.6)	0	1 (0.4)
Progressive Disease	54 (56.3)	63 (64.9)	68 (43.0)	93 (58.9)	122 (48.0)	156 (61.2)
Protocol Deviation	0	0	2 (1.3)	1 (0.6)	2 (0.8)	1 (0.4)
Withdrawal by Participant	14 (14.6)	9 (9.3)	26 (16.5)	18 (11.4)	40 (15.7)	27 (10.6)
Other	5 (5.2)	11 (11.3)	16 (10.1)	14 (8.9)	21 (8.3)	25 (9.8)

Table 96: Reasons for Early Discontinuation of Zolbetuximab/Placebo Treatment in Caucasian and Asian Subgroups Integrated analysis SPOTLIGHT/GLOW (SAS)

	Early Withdrawal (< 9 Weeks of Zolbetuximab Treatment)			
	Integrated SPOTLIGHT/GLOW			
	Caucasian		Asian	
Reason for Early Discontinuation	Arm A N=53	Arm B N=26	Arm A N=35	Arm B N=27
Adverse Event	24 (45.3)	2 (7.7)	7 (20.0)	6 (22.2)
Death	6 (11.3)	8 (30.8)	4 (11.4)	8 (29.6)
Lost to Follow-Up	1 (1.9)	0	0	0
Progressive Disease	6 (11.3)	13 (50.0)	6 (17.1)	7 (25.9)
Protocol Deviation	0	0	2 (5.7)	0
Withdrawal by Participant	12 (22.6)	2 (7.7)	12 (34.3)	4 (14.8)
Other	4 (7.5)	1 (3.8)	4 (11.4)	2 (7.4)

Table 97: TEAEs Leading to Interruption or Permanent Discontinuation of Zolbetuximab/Placebo in Caucasian and Asian Subgroups and Overall Population

Integrated SPOTLIGHT/GLOW Analysis						
	Caucasian		Asian		Overall Population	
Parameter SOC, n (%) PT, n (%)	Arm A N=232	Arm B N=222	Arm A N=253	Arm B N=250	Arm A N=533	Arm B N=527
Treatment-Emergent Adverse Events Leading to Interruption of Zolbetuximab/Placebo						
Overall	168 (72.4)	95 (42.8)	145 (57.3)	64 (25.6)	348 (65.3)	182 (34.5)
Gastrointestinal disorders	126 (54.3)	15 (6.8)	76 (30.0)	7 (2.8)	225 (42.2)	26 (4.9)
Vomiting	80 (34.5)	6 (2.7)	58 (22.9)	2 (0.8)	150 (28.1)	9 (1.7)
Nausea	88 (37.9)	4 (1.8)	41 (16.2)	0	147 (27.6)	5 (0.9)
Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Zolbetuximab/Placebo						
Overall	59 (25.4)	25 (11.3)	37 (14.6)	32 (12.8)	106 (19.9)	66 (12.5)
Gastrointestinal disorders	28 (12.1)	4 (1.8)	13 (5.1)	11 (4.4)	46 (8.6)	17 (3.2)
Vomiting	11 (4.7)	1 (0.5)	5 (2.0)	2 (0.8)	20 (3.8)	3 (0.6)
Nausea	9 (3.9)	0	6 (2.4)	2 (0.8)	18 (3.4)	2 (0.4)

Table 98: TEAEs Leading to Early Permanent Discontinuation of Zolbetuximab/Placebo in Caucasian and Asian Subgroups and Overall Population (SAS, Subjects who Discontinued Treatment within 9 Weeks)

Integrated SPOTLIGHT/GLOW Analysis						
Reason for Permanent Discontinuation SOC, n (%) PT, n (%)	Caucasian		Asian		Overall Population	
	Arm A N=53	Arm B N=26	Arm A N=35	Arm B N=27	Arm A N=101	Arm B N=60
Overall	31 (58.5)	9 (34.6)	9 (25.7)	13 (48.1)	47 (46.5)	24 (40.0)
Gastrointestinal disorders	17 (32.1)	3 (11.5)	6 (17.1)	3 (11.1)	27 (26.7)	7 (11.7)
Vomiting	11 (20.8)	1 (3.8)	3 (8.6)	1 (3.7)	17 (16.8)	2 (3.3)
Nausea	7 (13.2)	0	2 (5.7)	1 (3.7)	11 (10.9)	1 (1.7)

- By race and medical condition (GC/GEJ)

Table 99: TEAEs Leading to Interruption or Permanent Discontinuation of Zolbetuximab/Placebo in Caucasian-GEJ, Asian-GEJ, Caucasian-GC and Asian-GC Subgroups)

Integrated SPOTLIGHT/GLOW Analysis								
Parameter SOC, n (%) PT, n (%)	**Caucasian-GEJ**		**Asian-GEJ**		**Caucasian-GC**		**Asian-GC**	
	Arm A N=56	**Arm B N=71**	**Arm A N=27**	**Arm B N=28**	**Arm A N=176**	**Arm B N=151**	**Arm A N=226**	**Arm B N=222**
Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Zolbetuximab/Placebo								
Overall	14 (25.0)	8 (11.3)	3 (11.1)	2 (7.1)	45 (25.6)	17 (11.3)	34 (15.0)	30 (13.5)
Gastrointestinal disorders	7 (12.5)	2 (2.8)	1 (3.7)	0	21 (11.9)	2 (1.3)	12 (5.3)	11 (5.0)
Nausea	2 (3.6)	0	1 (3.7)	0	7 (4.0)	0	5 (2.2)	2 (0.9)
Vomiting	2 (3.6)	0	1 (3.7)	0	9 (5.1)	1 (0.7)	4 (1.8)	2 (0.9)
Treatment-Emergent Adverse Events Leading to Interruption of Zolbetuximab/Placebo								
Overall	40 (71.4)	32 (45.1)	11 (40.7)	2 (7.1)	128 (72.7)	63 (41.7)	134 (59.3)	62 (27.9)
Gastrointestinal disorders	29 (51.8)	3 (4.2)	5 (18.5)	0	97 (55.1)	12 (7.9)	71 (31.4)	7 (3.2)
Nausea	25 (44.6)	1 (1.4)	4 (14.8)	0	63 (35.8)	3 (2.0)	37 (16.4)	0
Vomiting	17 (30.4)	1 (1.4)	3 (11.1)	0	63 (35.8)	5 (3.3)	55 (24.3)	2 (0.9)

- By medical condition (GC/GEJ)

Table 100: End-of-Treatment Reasons in GC and GEJ Adenocarcinoma Subgroups – Discontinuation of Zolbetuximab/Placebo (FAS)

Parameter Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
GC						
n	219	210	219	209	438	419
Discontinuation						
No	38 (17.4)	29 (13.8)	28 (12.8)	16 (7.7)	66 (15.1)	45 (10.7)
Yes	181 (82.6)	181 (86.2)	191 (87.2)	193 (92.3)	372 (84.9)	374 (89.3)
Primary Study Drug Treatment Status						
Adverse Event	32 (14.6)	11 (5.2)	29 (13.2)	14 (6.7)	61 (13.9)	25 (6.0)
Death	8 (3.7)	11 (5.2)	20 (9.1)	18 (8.6)	28 (6.4)	29 (6.9)
Lost to Follow-Up	1 (0.5)	0	1 (0.5)	1 (0.5)	2 (0.5)	1 (0.2)
Progressive Disease	104 (47.5)	129 (61.4)	86 (39.3)	131 (62.7)	190 (43.4)	260 (62.1)
Protocol Deviation	0	0	2 (0.9)	1 (0.5)	2 (0.5)	1 (0.2)
Withdrawal by Participant	20 (9.1)	16 (7.6)	29 (13.2)	18 (8.6)	49 (11.2)	34 (8.1)
Pregnancy	0	0	0	0	0	0
Other	16 (7.3)	14 (6.7)	24 (11.0)	10 (4.8)	40 (9.1)	24 (5.7)
GEJ						
n	64	72	35	44	99	116
Discontinuation						
No	9 (14.1)	13 (18.1)	2 (5.7)	2 (4.5)	11 (11.1)	15 (12.9)
Yes	55 (85.9)	59 (81.9)	33 (94.3)	42 (95.5)	88 (88.9)	101 (87.1)
Primary Study Drug Treatment Status						
Adverse Event	10 (15.6)	3 (4.2)	5 (14.3)	1 (2.3)	15 (15.2)	4 (3.4)
Death	5 (7.8)	5 (6.9)	4 (11.4)	4 (9.1)	9 (9.1)	9 (7.8)
Lost to Follow-Up	0	0	0	0	0	0
Progressive Disease	29 (45.3)	48 (66.7)	16 (45.7)	26 (59.1)	45 (45.5)	74 (63.8)
Protocol Deviation	1 (1.6)	0	0	0	1 (1.0)	0
Withdrawal by Participant	9 (14.1)	2 (2.8)	6 (17.1)	5 (11.4)	15 (15.2)	7 (6.0)
Pregnancy	0	0	0	0	0	0
Other	1 (1.6)	1 (1.4)	2 (5.7)	6 (13.6)	3 (3.0)	7 (6.0)

Table 101: Reasons for Early Withdrawal from Zolbetuximab/Placebo Treatment in GC and GEJ Subgroups in Integrated Analysis SPOTLIGHT/GLOW (SAS)

Reason for Early Withdrawal	Early Withdrawal (< 9 Weeks of Zolbetuximab Treatment)			
	Integrated SPOTLIGHT and GLOW			
	GC		GEJ	
	Arm A N=81	Arm B N=44	Arm A N=20	Arm B N=16
Adverse Event	29 (35.8)	8 (18.2)	8 (40.0)	1 (6.3)
Death	8 (9.9)	14 (31.8)	4 (20.0)	3 (18.8)
Lost to Follow-Up	1 (1.2)	0	0	0
Progressive Disease	11 (13.6)	13 (29.5)	1 (5.0)	10 (62.5)

Reason for Early Withdrawal	Early Withdrawal (< 9 Weeks of Zolbetuximab Treatment)			
	Integrated SPOTLIGHT and GLOW			
	GC		GEJ	
	Arm A N=81	Arm B N=44	Arm A N=20	Arm B N=16
Protocol Deviation	2 (2.5)	0	0	0
Withdrawal by Participant	21 (25.9)	6 (13.6)	7 (35.0)	2 (12.5)
Other	9 (11.1)	3 (6.8)	0	0

Table 102: TEAEs Leading to Interruption or Permanent Discontinuation of Zolbetuximab/Placebo in GEJ and GC Subgroups and Overall Population)

Parameter, n (%)	GC		GEJ		Overall Population	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Treatment-Emergent Adverse Events Leading to Interruption of Zolbetuximab/Placebo						
Overall	283 (65.2%)	145 (35.0%)	65 (65.7%)	37 (32.7%)	348 (65.3%)	182 (34.5%)
Gastrointestinal disorders	183 (42.2%)	23 (5.6%)	42 (42.4%)	3 (2.7%)	225 (42.2%)	26 (4.9%)
Vomiting	126 (29.0%)	8 (1.9%)	24 (24.2%)	1 (0.9%)	150 (28.1%)	9 (1.7%)
Nausea	112 (25.8%)	4 (1.0%)	35 (35.4%)	1 (0.9%)	147 (27.6%)	5 (0.9%)
Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Zolbetuximab/Placebo						
Overall	87 (20.0%)	54 (13.0%)	19 (19.2%)	12 (10.6%)	106 (19.9%)	66 (12.5%)
Gastrointestinal disorders	37 (8.5%)	14 (3.4%)	9 (9.1%)	3 (2.7%)	46 (8.6%)	17 (3.2%)
Vomiting	16 (3.7%)	3 (0.7%)	4 (4.0%)	0	20 (3.8%)	3 (0.6%)
Nausea	15 (3.5%)	2 (0.5%)	3 (3.0%)	0	18 (3.4%)	2 (0.4%)

Table 103: TEAEs Leading to Early Permanent Discontinuation of Zolbetuximab/Placebo in GC and GEJ Subgroups and Overall Population: Integrated SPOTLIGHT/GLOW (Participants who Discontinued Treatment < 9 Weeks)

Reason for Permanent Discontinuation, n (%)	GC		GEJ		Overall Population	
	Arm A N=81	Arm B N=44	Arm A N=20	Arm B N=16	Arm A N=101	Arm B N=60
Overall	39 (48.1)	19 (43.2)	8 (40.0)	5 (31.3)	47 (46.5)	24 (40.0)
Gastrointestinal disorders	22 (27.2)	5 (11.4)	5 (25.0)	2 (12.5)	27 (26.7)	7 (11.7)
Vomiting	14 (17.3)	2 (4.5)	3 (15.0)	0	17 (16.8)	2 (3.3)
Nausea	9 (11.1)	1 (2.3)	2 (10.0)	0	11 (10.9)	1 (1.7)

Analyses to evaluate the influence of lower exposure due to lower exposure due to discontinuations/ dose interruptions on the treatment effect in the Overall population and by race subgroup*:*

Table 104: Descriptive Summary of Relative Exposure Intensity (REI) of Zolbetuximab/Placebo for SPOTLIGHT/GLOW (SAF)

Parameter	Category/ Statistic	Arm A (N=533)	Arm B (N=527)	Total (N=1060)
Relative Exposure Intensity (%) [1]	n	532	527	1059
	Mean	90.666	95.403	93.023
	SD	17.599	9.823	14.458
	Min	6.40	3.49	3.49
	Median	95.522	100.00	99.422
	Max	184.18	200.00	200.00
Relative Exposure Intensity < 75%, n (%)		56 (10.5)	8 (1.5)	64 (6.0)
Relative Exposure Intensity ≥ 75%, n (%)		476 (89.3)	519 (98.5)	995 (93.9)
Missing		1	0	1

Arm A = Zolbetuximab + mFOLFOX6/CAPOX, Arm B = Placebo + mFOLFOX6/CAPOX. SAF: safety analysis set.
[1] (Actual cumulative dose/planned cumulative dose) × 100%. Planned cumulative dose is defined as (800 + 600 × [Number of Planned Dosing −1]). The number of planned dosing takes into consideration the duration of treatment on protocol with zolbetuximab/placebo and defined as ([duration of zolbetuximab/placebo]/21-day dosing interval) and calculated by ceiling up to an integer value.

Table 105: Summary of Participants with TEAEs Leading to Dose Interruption or Withdrawal of Any Study Drug for Overall Population, Race = Caucasian, and Race = Asian in SPOTLIGHT/GLOW (FAS)

Parameter	Category/ Statistic	Overall Population			Race = White			Race = Asian		
		Arm A (N=537)	Arm B (N=535)	Total (N=1072)	Arm A (N=234)	Arm B (N=224)	Total (N=458)	Arm A (N=254)	Arm B (N=255)	Total (N=509)
The Number of Participants who had TEAE Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab	Yes (n, %)	51 (9.5)	6 (1.1)	57 (5.3)	33 (14.1)	4 (1.8)	37 (8.1)	12 (4.7)	1 (0.4)	13 (2.6)
	No (n, %)	486 (90.5)	529 (98.9)	1015 (94.7)	201 (85.9)	220 (98.2)	421 (91.9)	242 (95.3)	254 (99.6)	496 (97.4)
The Number of Participants who had TEAE Leading to Withdrawal of any Study Drug with Zolbetuximab Treatment Discontinued within 180 days	Yes (n, %)	91 (16.9)	70 (13.1)	161 (15.0)	51 (21.8)	22 (9.8)	73 (15.9)	30 (11.8)	39 (15.3)	69 (13.6)
	No (n, %)	446 (83.1)	465 (86.9)	911 (85.0)	183 (78.2)	202 (90.2)	385 (84.1)	224 (88.2)	216 (84.7)	440 (86.4)
The Number of Participants who had TEAE Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab or TEAE Leading to Withdrawal of any Study Drug with Zolbetuximab Treatment Discontinued within 180 days	Yes (n, %)	116 (21.6)	76 (14.2)	192 (17.9)	66 (28.2)	26 (11.6)	92 (20.1)	36 (14.2)	40 (15.7)	76 (14.9)
	No (n, %)	421 (78.4)	459 (85.8)	880 (82.1)	168 (71.8)	198 (88.4)	366 (79.9)	218 (85.8)	215 (84.3)	433 (85.1)

Table 106: Summary of Median PFS and OS Duration in Zolbetuximab Group (SPOTLIGHT/GLOW) by TEAEs Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab or TEAE Leading to Withdrawal of any Study Drug with Zolbetuximab Treatment Discontinuation within 180 Days: Overall Population, Race = Caucasian, and Race = Asian

Measure	Overall Survival		Progression-Free Survival	
	Defined AE Dose Interruption/Drug Withdrawal Event [1]		Defined AE Dose Interruption/Drug Withdrawal Event [1]	
	Yes	No	Yes	No
Overall Population	N=116	N=421	N=116	N=421
Median (95% CI) (Months) [2]	8.54 (7.23, 10.28)	18.60 (16.69, 20.63)	5.09 (4.30, 7.46)	10.41 (8.94, 12.35)
Race = White	N=66	N=168	N=66	N=168
Median (95% CI) (Months) [2]	8.84 (7.20, 11.66)	17.87 (15.80, 22.90)	4.93 (4.24, 7.95)	9.69 (8.34, 12.42)
Race = Asian	N=36	N=218	N=36	N=218
Median (95% CI) (Months) [2]	7.89 (3.88, 15.51)	18.83 (16.49, 23.10)	4.99 (3.61, 15.51)	12.09 (9.43, 13.47)

REI: relative exposure index
[1] TEAE Leading to Dose Interruption of any Study Drug with < 75% REI of zolbetuximab or TEAE Leading to withdrawal of any study drug with zolbetuximab
treatment discontinued within 180 days. The patients who were not dosed with any study drug were included in Defined AE Dose Interruption/Drug Withdrawal
Event = No.
[2] Based on Kaplan-Meier estimate.

Table 107: Summary of Participants with Nausea or Vomiting Leading to Dose Interruption or Withdrawal of Any Study Drug for Overall Population, Race = Caucasian, and Race = Asian in SPOTLIGHT/GLOW

Parameter	Category/ Statistic	Overall Population			Race = White			Race = Asian		
		Arm A (N=537)	Arm B (N=535)	Total (N=1072)	Arm A (N=234)	Arm B (N=224)	Total (N=458)	Arm A (N=254)	Arm B (N=255)	Total (N=509)
The Number of Participants who had Nausea and Vomiting Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab/Placebo	Yes (n, %)	42 (7.8)	1 (0.2)	43 (4.0)	28 (12.0)	1 (0.4)	29 (6.3)	9 (3.5)	0	9 (1.8)
	No (n, %)	495 (92.2)	534 (99.8)	1029 (96.0)	206 (88.0)	223 (99.6)	429 (93.7)	245 (96.5)	255 (100.0)	500 (98.2)
The Number of Participants who had Nausea and Vomiting Leading to Withdrawal of any Study Drug with Zolbetuximab/Placebo Treatment Discontinued within 180 days	Yes (n, %)	29 (5.4)	4 (0.7)	33 (3.1)	16 (6.8)	1 (0.4)	17 (3.7)	8 (3.1)	3 (1.2)	11 (2.2)
	No (n, %)	508 (94.6)	531 (99.3)	1039 (96.9)	218 (93.2)	223 (99.6)	441 (96.3)	246 (96.9)	252 (98.8)	498 (97.8)
The Number of Participants who had Nausea and Vomiting Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab/Placebo or Nausea and Vomiting Leading to Withdrawal of any Study Drug with Zolbetuximab/Placebo Treatment Discontinued within 180 days	Yes (n, %)	60 (11.2)	5 (0.9)	65 (6.1)	37 (15.8)	2 (0.9)	39 (8.5)	14 (5.5)	3 (1.2)	17 (3.3)
	No (n, %)	477 (88.8)	530 (99.1)	1007 (93.9)	197 (84.2)	222 (99.1)	419 (91.5)	240 (94.5)	252 (98.8)	492 (96.7)

Table 108: Summary of OS and PFS by Censoring Nausea or Vomiting Leading to Dose Interruption of any Study Drug with < 75% REI of Zolbetuximab or Nausea and Vomiting Leading to Withdrawal of any Study Drug with Zolbetuximab Treatment Discontinuation within 180 Days for Overall Population, Race = Caucasian, and Race = Asian in SPOTLIGHT/GLOW (FAS)

	Overall Survival		Progression-Free Survival	
Measure	Arm A	Arm B	Arm A	Arm B
Overall Population	N=537	N=535	N=537	N=535
Median (95% CI) Duration (Months) [1]	17.94 (16.43, 19.78)	13.67 (12.29, 15.01)	10.38 (8.71, 12.22)	8.18 (7.52, 8.34)
Stratified Analysis Hazard Ratio (95% CI) [2]	0.661 (0.562, 0.779)		0.650 (0.550, 0.767)	
Race = White	N=234	N=224	N=234	N=224
Median (95% CI) Duration (Months) [1]	17.54 (15.80, 21.68)	14.69 (13.60, 16.03)	9.17 (8.34, 12.42)	8.67 (8.11, 10.22)
Stratified Analysis Hazard Ratio (95% CI) [2]	0.765 (0.594, 0.985)		0.799 (0.620, 1.028)	
Race = Asian	N=254	N=255	N=254	N=255
Median (95% CI) Duration (Months) [1]	18.23 (16.36, 21.49)	13.11 (11.37, 14.85)	10.41 (8.64, 12.68)	7.23 (6.24, 8.15)
Stratified Analysis Hazard Ratio (95% CI) [2]	0.618 (0.490, 0.778)		0.545 (0.427, 0.694)	

Table 109: Cumulative Incidence Rate in Zolbetuximab Group for TEAE Leading to Dose Interruption of any Study Drug with < 75 REI of Zolbetuximab or TEAE Leading to Withdrawal of any Study Drug with the Subjects who Discontinued Zolbetuximab Treatment within 180 days with OS as Censor by Race Full Analysis Set (CL-0301/CL-0302) Race = Caucasian

Measure	Z 800/600 mg/m2 + mFOLFOX6/ CAPOX (N=234)
Competing Events [1], n (%)	66 (28.2%)
Censored [2], n (%)	168 (71.8%)
Cumulative Incidence Rate of Competing Events [1], % (95% CI)	
At 12 months	24.84% (18.74%, 31.40%)
At 18 months	36.78% (28.72%, 44.84%)
At 24 months	42.40% (33.21%, 51.29%)
At 30 months	50.52% (35.79%, 63.53%)
At 36 months	50.52% (35.79%, 63.53%)

Table 110: Cumulative Incidence Rate in Zolbetuximab Group for TEAE Leading to Dose Interruption of any Study Drug with < 75 REI of Zolbetuximab or TEAE Leading to Withdrawal of any Study Drug with the Subjects who Discontinued Zolbetuximab Treatment within 180 days with OS as Competing Events of it by Race Full Analysis Set (CL-0301/CL-0302) Race = Caucasian

Measure	Z 800/600 mg/m2 + mFOLFOX6/ CAPOX (N=234)
Competing Events [1], n (%)	66 (28.2%)
Deaths [2], n (%)	84 (35.9%)
Censored, n (%)	84 (35.9%)
Cumulative Incidence Rate of Competing Events [1], % (95% CI)	
At 12 months	22.01% (16.66%, 27.84%)
At 18 months	30.14% (23.74%, 36.77%)
At 24 months	33.24% (26.43%, 40.19%)
At 30 months	35.84% (28.32%, 43.40%)
At 36 months	35.84% (28.32%, 43.40%)

2.6.5.8. Supportive studies

FAST Study (GM-IMAB-001-03)

The FAST study was a randomized, open-label, phase 2, proof-of-concept study, evaluating the efficacy and safety of zolbetuximab in combination with EOX (Epirubicin, Oxaliplatin, Capecitabine) as first-line therapy in participants with CLDN18.2-positive advanced gastric/GEJ/esophageal adenocarcinoma.

Main inclusion criteria:

- Histologically confirmed, inoperable locally advanced disease or resections with macroscopic residual disease at the resection margin or recurrent or metastatic disease.
- CLDN18.2 expression confirmed by immunohistochemistry in paraffin-embedded tumor tissue sample. Any tumor with a staining intensity of 2+ or 3+ (the sum was decisive) in at least 40% of the tumor cells. *Note*: determination based on CLAUDETECT TM 18.2 Histology Kit
- HER2-negative patients and patients with HER2-positive status but not eligible for trastuzumab therapy by discretion of the investigator.

Main exclusion criteria:

- Previous chemotherapy for advanced disease; previous perioperative chemotherapy with curative intention within 6 months of the start of study treatment.

Randomization was stratified by CLDN18.2 positivity (≥ 70% of the tumor cells stained vs < 70% of the tumor cells stained) and presence of non-measurable vs measurable disease at baseline.

Participants were randomized to one of 3 treatment arms:

Arm 1: EOX* alone Q3W (84 participants)

Arm 2: zolbetuximab 800 mg/m^2 (loading dose) /600 mg/m^2 (subsequent cycles) with EOX Q3W (77 participants)

Arm 3: zolbetuximab 1000 mg/m^2 with EOX Q3W (85 participants)

* Epirubicin 50 mg/m2 IV, oxaliplatin 130 mg/m² IV, capecitabine 625 mg/m² oral

Initially, participants were randomized to either EOX alone (Arm 1) or zolbetuximab plus EOX (Arm 2). The study was subsequently extended to investigate a higher dose of zolbetuximab (Arm 3). Arm 3 was started after approximately 60 participants in Arm 1 and Arm 2 had been randomized in a 1:1 ratio. The randomization ratio was adjusted to 1:1:7 to allow recruitment in Arm 3 to catch up with the other 2 arms and was then adjusted once more to 1:1:1 to reach the planned number of participants (at least 70 evaluable participants per arm).

Primary efficacy objectives/endpoints: PFS

Secondary objectives/endpoints: OS, survival status at 12 months, TTP, ORR, DCR and DOR

Results:

Baseline Characteristics

Most participants were Caucasian (95.9%) and male (65.0%), had gastric tumor (84.1%), metastatic disease (95.9%) and measurable disease (77.2%). The median age was 58.5 years (range: 22 to 77 years). The majority of patients had ≥ 70% CLDN18.2-stained cells (74.4%).

Efficacy outcome in **overall** study population (final analysis, data cutoff date 31 Jan 2019):

Primary endpoint - **PFS**

Table 111: PFS assessed by IRC – FAS (FAST)

	Arm 1 EOX alone (n = 84)	Arm 2 Zolbetuximab 800/600 mg/m^2 plus EOX (n = 77)	Arm 3 Zolbetuximab 1000 mg/m^2 plus EOX (n = 85)
Censoring Summary†, n (%)			
Patients with event	62 (73.8)	42 (54.5)	49 (57.6)
Censored patients	22 (26.2)	35 (45.5)	36 (42.4)
Kaplan-Meier Estimates, months			
Median (95% CI)	5.3 (4.1, 7.1)	7.5 (5.6, 11.3)	7.1 (5.6, 8.0)
PFS rate 18 months	2.1%	27.5%	12.0%
Treatment Comparison vs EOX Alone			
Hazard ratio (95% CI) ‡	NA	0.44 (0.29, 0.67)	0.58 (0.39, 0.85)
Log-rank test P value§		< 0.0005	0.0114
Treatment Comparison vs Zolbetuximab 1000 mg/m^2 plus EOX			
Hazard ratio (95% CI) ‡	NA	0.76 (0.49, 1.18)	NA
Log-rank test P value§		0.2842	

All participants who were randomized and who received at least 1 dose of any study medication (FAS – full analysis set).
PFS was defined as the time from randomization to the first observation of PD (assessed by IRC) or death from any cause.

† Patients who did not have documented PD or death were censored as of the last tumor evaluation when they were alive and progression-free.
‡ Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs non-measurable disease at baseline and by the number of CLDN18.2-stained cells categorized as < 70% vs ≥ 70%.
§ The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1, and a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

Secondary endpoints

Overall Survival

Table 112: Overall Survival – FAS – Final Analysis (data cutoff 31 Jan 2019; excerpt)

Category Parameter/Statistics	Overall		
	Arm 1 EOX alone (n = 84)	**Arm 2 Zolbetuximab 800/600 mg/m² plus EOX (n = 77)**	**Arm 3 Zolbetuximab 1000 mg/m² plus EOX (n = 85)**
Censoring Summary, n (%)			
Patients with event	79 (94.0)	63 (81.8)	77 (90.6)
Censored patients	5 (6.0)	14 (18.2)	8 (9.4)
Median (95% CI)	8.3 (6.9, 10.2)	13.0 (9.7, 18.7)	9.6 (8.3, 11.4)
OS rate 18 months	10.0%	39.0%	26.2%
Treatment Comparison vs EOX Alone			
Hazard ratio (95% CI)	NA	0.55 (0.39, 0.77)	0.75 (0.55, 1.04)
Log-rank test P value		< 0.0005	0.1292
Treatment Comparison vs Zolbetuximab 1000 mg/m2 plus EOX			
Hazard ratio (95% CI)	NA	0.73 (0.52, 1.02)	NA
Log-rank test P value		0.1280	

ORR (Objective Response rate, by IRC, confirmed): 25% vs 39% vs 31% for arms 1, 2 and 3, respectively.

For results of prespecified exploratory subgroup analyses based on < 70% and ≥ 70% CLDN18.2-positivity in a participant's tumor sample, please see section "In vitro biomarker test for patient selection for efficacy".

ILUSTRO Study (GM-IMAB-001-03)

ILUSTRO is an ongoing open-label, multi-arm, nonrandomized study to assess the antitumor activity of zolbetuximab, as monotherapy or combination therapy, in participants with metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma whose tumours were CLDN18.2-positive, determined by central IHC testing.

Presentation of data focus on Cohort 2 only, as the participant population and treatment regimen in this cohort are similar to those in the SPOTLIGHT study.

Treatment Group (n)	**Treatment**	**Line of Treatment**	**CLDN18.2 Positivity Cutoff**	**HER2 Status**	**PD-L1 Status**
Cohort 2 (n=21)	Zolbetuximab + mFOLFOX6	First-line	High	HER2-negative	Not applicable

High: ≥ 75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining determined by central IHC testing.

Zolbetuximab was applied with an 800 mg/m2 loading dose followed by subsequent doses of 600 mg/m2 Q3W.

Most participants were either Caucasian (44.4%) or Asian (50.0%), median age was 63 year, 19.0% of participants had received prior neoadjuvant or adjuvant chemotherapy at least 6 months prior to the first dose of study treatment.

Efficacy results

Table 113: Overview of efficacy results (by ICR- FAS; ILUSTRO Cohort 2)

	Cohort 2 Zolbetuximab 800/600 mg/m² plus mFOLFOX6 (n = 21)
ORR, Confirmed, n (%)	15 (**71.4**)
95% CI	(47.82, 88.72)
Duration of Response, Confirmed, months	
Median (95% CI) ‡	15.9 (5.4, NE)
PFS (months)	
Median (95% CI)	**17.81** (8.05, 25.69)

Data cutoff: 03 May 2021.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Two global, randomized, double-blind and placebo-controlled phase 3 studies evaluated zolbetuximab in combination with fluoropyrimidine- and platinum containing chemotherapy as first line treatment in participants with locally advanced unresectable or metastatic HER2 negative gastric (GC) or gastroesophageal junction (GEJ) adenocarcinoma whose tumors were CLDN18.2-positive.

CLDN18.2-positive tumors were defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining based on central IHC assessment using the investigational VENTANA CLDN18 (43-14A) RxDx Assay. The decision to exclude patients with low CLDN18 in both pivotal studies cannot be followed. As already pointed out in in the Scientific Advice (EMEA/H/SA/3652/1/2017/III) data for subjects with low CLDN18.2 expression levels are not available, since already the FAST study included only subjects with an expression ≥40%; subjects in the monotherapy study were included with CLDN18.2 expression ≥50%.

Pooled efficacy data (pooled analyses of Arms 2 and 3 with zolbetuximab doses of 800/600 mg/m² and 1000 mg/m² + EOX) according to CLDN18.2 expression from the FAST study did not show a predictive value of CLDN18.2 expression of <70%/≥70%: HR PFS (95% CI) 0.48 (0.24, 0.78) vs. 0.52 (0.35, 0.77); OS (95% CI) 0.66 (0.37, 1.15) vs. 0.62 (0.44, 0.87). (Of note: CLDN18.2-positive tumors defined as ≥ 70% by the clinical trial assay used in FAST correspond to ≥ 75% of positive tumor cells using the CLDN18 (43-14A) RxDx Assay). However, the applicant further justified that data from Arm 3 were not as reliable, therefore, only the first 2 Arms were considered. Indeed, a predictive value for this cut-off could be anticipated. For participants with ≥ 70% of tumor cells staining for CLDN18.2 at baseline, the median OS was 7.6 months longer in Arm 2 compared with Arm 1 (16.5 vs 8.9 months, respectively), with an HR of 0.50 (95% CI: 0.33, 0.74). In contrast, for participants with < 70% of tumor cells staining for CLDN18.2 at baseline (63 participants in total, 25 in Arm 1, 20 in Arm 2, and 18 in Arm 3), the median OS was only 1 month longer (8.3 vs 7.4 months, respectively). The HR was 0.78 [95% CI: 0.40, 1.49]). Nevertheless, numbers of enrolled patients with CLDN18.2 staining in < 70% of cells in the FAST study were very limited (n=20).

Participants in the SPOTLIGHT study received zolbetuximab or placebo in combination with mFOLFOX6 (n=565); the GLOW study evaluated zolbetuximab plus CAPOX compared with placebo plus CAPOX (n=507). Duration of therapy was "until disease progression or unacceptable toxicity". The chemotherapy backbone regimens of mFOLFOX6 and CAPOX are included in current clinical guidelines

as possible 1L GEJ/gastric cancer treatment options and were agreed on during previous EMA SA. The applied indication wording "in combination with fluoropyrimidine- and platinum-containing chemotherapy" principally also refers to regimens with cisplatin as platinum compound that had not been evaluated in the pivotal trials. Both cisplatin and oxaliplatin have shown to be equally effective in RCTs, thus extrapolation of efficacy data from the used oxaliplatin regimens (in combination with 5-FU or capecitabine) can be considered acceptable. It is however noted that both platinum compounds have a different safety profile and the combination of zolbetuximab with cisplatin might be more emetogenic as compared to the combination with oxaliplatin.

Zolbetuximab was administered intravenously as an 800 mg/m² loading dose followed by subsequent doses of 600 mg/m² every 3 weeks. The same Q3W dosage regimen was used in both pivotal studies. The Applicant seeks approval of an alternative two-weekly dose regimen of 400 mg/m² based on PK modelling to align administration with the two-weekly FOLFOX regimen (please be referred to section clinical pharmacology).

Randomization of participants (1:1) was stratified by region (Asia vs non-Asia), number of organs with metastatic sites (0 to 2 vs ≥ 3) and prior gastrectomy (Yes or No). The choice of stratification factors can be followed.

The selected eligibility criteria were overall acceptable to select a study population representative for the target population, apart from the typical limitations to restrict enrolment to patients with good performance status and adequate organ function. Baseline and disease characteristics were generally balanced between treatment arms for both studies. Across both studies the majority of participants (67%) were <65 years of age (median age was 60.5 years) and only 6% were enrolled with an age above 75 years. Participants were primarily male (62%), the majority had an ECOG PS of 1 (57%) and were Caucasian (45%) or Asian (50%); Hispanic (9%) and Black participants (0.7%) were underrepresented. About half of the participants were former or current smokers. Most participants had adenocarcinoma of the stomach (80%) and had not received prior gastrectomy/esophagectomy (71%). Locally advanced disease at study entry was reported for 16% and 12% of participants in SPOTLIGHT and GLOW, respectively. Although baseline characteristics were overall similar between both pivotal studies, a different regional recruitment is noted. While the majority of patients were in the non-Asian region in SPOTLIGHT (68%), the GLOW study recruited mainly in the Asian region (62%). As expected given the higher proportion of Caucasian participants in SPOTLIGHT, slightly heavier patients and more patients with GEJ adenocarcinoma were recruited in the SPOTLIGHT study (median weight 63 kg vs 60 kg, median BMI 23 vs 22 kg/m², GEJ adenocarcinoma 24% vs 16%). In SPOTLIGHT a slighter higher proportion of GEJ adenocarcinoma were reported to be GEJ distal as compared to GLOW: 37% of GEJ (n=50) vs 29% of GEJ (n=23). Barrett Oesophagus were reported in 3.2% vs 1.4% of patients in SPOTLIGHT vs GLOW (however, 37% were unknown).

Predefined endpoints and statistical analysis were similar in both studies. The primary endpoint was PFS assessed by independent review (IRC), with OS as key secondary endpoint. TTCD (described as key secondary endpoint in the study protocol, but not included in the multiplicity control) was defined as the time to first confirmed deterioration of physical function (PF), abdominal pain/discomfort (OG25-Pain) and Global Health Status/Quality of Life (GHS/QoL). Other secondary endpoints were overall response rates (ORR), duration of response (DOR) and additional Health Related Quality of Life (HRQoL) parameters as measured by EORTC QLQ-C30, QLQ-OG25 (plus STO22 Belching for GLOW), Global Pain and EQ-5D-5L questionnaires. The choice of PFS as primary endpoint and OS as key secondary endpoint was agreed on by CHMP in the EMA SA. The data were appropriately analysed (via Kaplan-Meier curves, log-rank tests, Cox models with covariate adjustment and several prespecified sensitivity and subgroup analyses), and so was the hierarchical testing strategy (OS to be analysed only if PFS significant at one-sided 0.025 alpha level).

Several protocol amendments were introduced similarly across both studies that mainly served to improve safety by clarifying eligibility criteria and dose modifications, or allowed recruitment of patients with non-measurable disease. Protocol versions 5.0 (Oct 2021) reduced the number of PFS events required for the interim analysis of overall survival to 300 (368 planned in SPOTLIGHT and 344 in GLOW). The reduced number of PFS events still allowed to test the primary endpoint of PFS at >93% power, as both studies had been overpowered for PFS in order to have appropriate power (80%) for the key secondary OS endpoint. The same amendment removed the Per Protocol Set (PPS) analysis, which is questionable, as this analysis would provide information about the efficacy of the product under best conditions. However, given the results of the FAS analysis and the sensitivity analyses, this omission is not considered critical.

Major protocol deviations were reported for 27.5% participants in study SPOTLIGHT and for 21.5% in study GLOW; however, the nature of these did not raise concerns regarding the validity of the study results. Likewise, the study conduct during the COVID-19 pandemic did not appear to have a major impact on the study integrity.

Efficacy data and additional analyses

Patient's disposition data reflect the poor prognosis of these patients: at DCO in SPOTLIGHT 83.4% (zolbetuximab) vs. 85.1% (placebo) of patients had discontinued treatment with zolbetuximab/placebo; being 88.2% (zolbetuximab) vs. 92.9% (placebo) in GLOW. Therefore, most patients at DCO had discontinued treatment with zolbetuximab. In SPOTLIGHT only 28% patients (N=78) remained on treatment with zolbetuximab for longer than 48 weeks (around 1 year); being 17.7% (N=45) in GLOW. Only 14.7% (N=41) patients remained on zolbetuximab for longer than 72 weeks (around 18 months) in SPOTLIGHT; and 11% (N=28) in GLOW.

Both pivotal studies, SPOTLIGHT and GLOW, met their primary endpoint of PFS and key secondary endpoint of OS and demonstrated statistically significant improvements for the addition of zolbetuximab to standard of care chemotherapy in the overall study populations (based on final PFS analyses and IA for OS; DCO 09-Sep-2022 for SPOTLIGHT and 07-Oct-2022 for GLOW).

Study **SPOTLIGHT** reported a **PFS** HR of 0.75 (95% CI 0.598, 0.942), a difference in median PFS of 1.9 months, and a 10% PFS rate difference at 18 months. In study **GLOW,** the PFS HR was 0.687 (95% CI 0.544, 0.866) and the difference in median PFS was 1.4 months with a 19% PFS rate difference at 12 months (difference 13% at 18 months with low numbers at risk). The prespecified sensitivity analyses of PFS including investigator-based assessment and analyses to address likely informative censoring showed overall consistent results and generally supported the robustness of the primary PFS analysis in both studies.

The survival benefit in study **SPOTLIGHT** was based on a HR of 0.75 (95% CI 0.6, 0.94), a 2.7 months improvement of median **OS** and a 10% OS rate difference at 24 months. Study **GLOW** reported an OS HR of 0.771 (95% CI: 0.615, 0.965), a 2.2 months improvement of median OS and a 10% OS rate difference at 18 months. The information fraction was 82% for both SPOTLIGHT and GLOW. Of note, OS results did not seem to have been impacted by differences in post-progression therapies. Most frequent post-progression therapies were paclitaxel (17% vs 19.5% and 18.1% vs 20.2% for zolbetuximab vs placebo in SPOTLIGHT and GLOW) and ramucirumab (12.4% vs 12.1% and 8.3% vs 11.1% for zolbetuximab vs placebo in SPOTLIGHT and GLOW).

In SPOTLIGHT, OS KM curves separate rather late after about 10 months but remain separated thereafter, an earlier separation of the OS curves was observed in GLOW. For both studies the improvements in overall survival can be considered clinically meaningful to support the benefit of zolbetuximab in the overall study populations.

The final OS and updated PFS analyses were provided for SPOTLIGHT during the procedure; the HRs for PFS (0.73; 95% CI: 0.59, 0.91) and for OS (HR=0.78; 95%CI: 0.64, 0.95) were consistent with the primary analysis based on a data cutoff date of 08 Sep 2023. The Applicant also provided final OS data and updated PFS results for GLOW that showed a sustained OS and PFS improvement: OS HR 0.76 (95% CI 0.62, 0.94), PFS HR 0.69 (95% CI 0.55, 0.86) (DCO 12 Jan 2024).

The secondary objective **TTCD** of PF, OG25-Pain and GHS/QoL showed no meaningful differences between treatment arms, although the final analysis is pending (TTCD was evaluated based on a threshold obtained from existing literature because the results from a noninterventional exit survey [8951-CL-0303] are pending). Similarly, the total and subscale mean scores of other HRQoL measures showed overlapping confidence intervals between both arms.

ORR and DOR based on unconfirmed responses as assessed by independent review (pre-specified secondary endpoints) did not show meaningful differences between treatment arms in both pivotal studies. A favourable effect of zolbetuximab was only reported in selected sensitivity analyses (in study GLOW only regarding response duration and in study SPOTLIGHT regarding ORR and DOR only by investigator assessment). In addition, results of the exploratory endpoint DCR (which includes the percentage of patients with SD) did not show any improvements by adding zolbetuximab to chemotherapy. DCR rates were 76% in both treatment arms in study GLOW and even higher in the placebo arm than in the zolbetuximab arm in study SPOTLIGHT (86.9% vs. 82.0%, respectively). Considering the postulated mode of action of ADCC and CDC, it does not appear plausible that zolbetuximab did not show any treatment effect on the tumour size. Exploratory analyses showed a trend for a more pronounced depth of response to treatment in the zolbetuximab treatment arms (best % change post baseline in tumour shrinkage). In addition, administration of zolbetuximab resulted in longer time to progression of PR, SD, or non-CR/non-SD in the zolbetuximab treatment group compared to placebo, which could account for the benefit in PFS/OS of zolbetuximab vs placebo. It is acknowledged that ORR does not always correlate to PFS and/or OS benefit in GC per literature [Shitara et al, 2014].

Exploratory endpoints of time to progression (TTP) and PFS2 indicated a benefit for the addition of zolbetuximab in both studies. Median time to date of progressive disease as assessed by the IRC was 17.8 vs 12.5 months in SPOTLIGHT and 12 vs 8.3 months in GLOW; median PFS2 was 14.2 vs 12 months in SPOTLIGHT and 11 vs 9 months in GLOW for zolbetuximab vs placebo, respectively (PFS2 HR 0.78 [95% CI 0.64, 0.96] in SPOTLIGHT and 0.71 [95% CI 0.58, 0.87] in GLOW).

Overall, the observed treatment effects of zolbetuximab (in view of favourable HRs of PFS and OS, the lack of a PRO or an ORR benefit and supporting exploratory endpoints of TTP and PFS2) were generally consistent across both studies; however, medians of PFS and OS as well as ORR, DCR and DOR were lower in the GLOW study compared to SPOTLIGHT for both treatment arms.

Directly comparing the outcome of placebo-treated participants between two different studies presents challenges. One of the differences was the higher proportion of Asian participants in the GLOW study. Pre-planned subgroup analysis revealed that the survival of placebo-treated participants in China was lower than the overall study population in both SPOTLIGHT and GLOW which might have contributed to the differences.

The Applicant conducted an **integrated efficacy analysis** across SPOTLIGHT and GLOW, which is considered appropriate given the similar study design and efficacy analyses. The integrated efficacy analysis across SPOTLIGHT and GLOW showed a PFS benefit in the combined phase 3 zolbetuximab group compared to treatment in the combined phase 3 control group: HR 0.72 (95% CI: 0.61, 0.85); median PFS 8.9 vs 8.2 months, difference of PFS rate at 18 months 11.5%. With a median follow-up time of almost 20 months in both groups the reported OS benefit was based on a HR of 0.76 (95% CI: 0.65, 0.89), median OS of 16.5 vs 13.6 months, and an approximately 10% difference of OS rate at 18

and 24 months in the combined phase 3 zolbetuximab group compared with the combined phase 3 control group. The TTCD (PF, OG25-Pain and GHS/QoL scores) as well as ORR and DOR per IRC were similar across both combined treatment groups. In conclusion, the efficacy analysis in the overall study population of the two pivotal studies SPOTLIGHT and GLOW demonstrated statistically significant improvements in PFS and OS that can be considered clinically meaningful to support a benefit for the addition of zolbetuximab to standard 1L chemotherapy in advanced GEJ/gastric cancer.

However, **subgroup** results of Caucasian and subjects with GEJ cancer (in particular in the small subgroup of distal GEJ carcinoma) raised concerns whether a relevant treatment effect and a favourable B/R can be expected in the European population (Caucasian: PFS and OS HR 0.92 [95% CI 0.7, 1.2]; GEJ: PFS HR 1.1 [95% CI 0.8, 1.6], OS HR 1.1 [95% CI 0.7, 1.5]; GEJ distal: PFS HR 1.4 [95% CI 0.8, 2.6], OS HR 1.6 [0.9, 2.9] in integrated analysis). Considering the large subgroup of Caucasian population (45%) and the consistently observed lower treatment effect across both endpoints of PFS and OS in both studies, the Applicant investigated possible factors that may have contributed to the HR differences observed in the subgroup analysis. Analyses of baseline/disease characteristics, biomarker (CLDN18.2) status, exposure-response models by race and a review of literature data could not sufficiently explain the differences. Data did not reveal a biological rationale for a different treatment effect in the Caucasian vs Asian or (distal) GEJ vs GEJ populations. Exploratory analysis by continent-geographical region showed a small trend towards a more favourable outcome in Europe (n=428 across both studies); the PFS HR of 0.85 (0.66, 1.10) and OS HR of 0.87 (00.67, 1.12) were closer to the HR demonstrated in the overall study population.

Analysis of Caucasian vs Asian

The Applicant concluded that the main factor that impacted efficacy was a difference in exposure to zolbetuximab (i.e. duration of exposure in days, median cumulative actual dose). This lower exposure in Caucasian compared to Asian participants (and in GEJ vs GC subgroups) was thought to be attributed to a higher rate of treatment discontinuation rate and dose interruptions in the zolbetuximab arm due to AEs, primarily nausea and vomiting. It is acknowledged that there appeared to be a consistent correlation of drug exposure with efficacy outcomes that could explain the different benefit in subgroups. The results for median cumulative actual dose, duration of zolbetuximab treatment, proportion of participants with >80% relative dose intensity, and proportion of patients with prematurely discontinued infusion indicated that the Caucasian subgroup received less zolbetuximab (and partly also less oxaliplatin) compared to the Asian subgroup. Indeed, a reduced exposure to zolbetuximab could be correlated with a lower treatment effect for Caucasian vs Asian, whereas an additional reduction of oxaliplatin exposure may lead to even detrimental effects (as seen in distal GEJ subgroup). It can be also agreed that higher rates of zolbetuximab discontinuations/interruptions have been observed in Caucasian as compared to Asian and this appears to be a plausible reason for the different exposure values.

To further substantiate that the observed differences in discontinuation/interruption rates were the reason for the different exposure and efficacy outcomes, the Applicant was requested to submit sensitivity analyses for PFS and OS in the overall population and by race for patients who had zolbetuximab discontinuations/interruptions due to AEs vs patients without discontinuations/interruptions. For these sensitivity analyses TEAEs leading to dose interruptions with a relative exposure intensity (REI) of <75% and/or TEAEs leading to discontinuation of zolbetuximab/placebo within 180 days were considered. The analyses confirmed the higher rate of dose interruptions and discontinuations in Caucasian vs Asian participants. Exploratory efficacy analyses suggest that PFS and OS were both affected and were lower regardless of race in participants who experienced TEAE leading to dose interruptions/discontinuations compared to those who did not experience such interruption or withdrawal of study drug (see Table 3.4.80).

The Applicant performed additional analyses to elucidate the association of adverse events with the treatment effect. Nausea or vomiting leading to dose interruption with < 75% REI of zolbetuximab/ placebo or TEAE leading to withdrawal of zolbetuximab/placebo within 180 days was defined as intercurrent event. Then, the treatment effect on PFS/OS was estimated as if TEAE leading to severe dose interruption or TEAE leading to early withdrawal would not occur. Results of these analyses suggest a hypothetical improvement in both PFS and OS, especially for the Caucasian population, the group with the higher incidence of experiencing such an intercurrent event. Despite the uncertainties on how the hypothetical assumptions affect the benefits of treatment, it can be concluded that <75% REI of zolbetuximab or TEAE leading to withdrawal of zolbetuximab within 180 days have an association with the risk of progression or death.

In summary, the Applicant provided several retrospective sensitivity analyses that have to be interpreted with caution. Nonetheless, the results of these additional analyses overall support the hypothesis that the lower exposure due to discontinuations/dose interruptions could be the main factor for the observed lower treatment effect in the Caucasian subgroup.

Information on the subgroup analyses with the difference in PFS and OS for Caucasian versus Asian patients has been reflected in section 5.1 of the SmPC.

Zolbetuximab is an add-on treatment, the uncertainties of lack of benefit in case of TEAEs may be acceptable, provided that it can be ensured that TEAEs are appropriately managed without impact on the exposure of the backbone treatment and that patients are appropriately followed (see also discussion on clinical safety).

Although it is not possible to fully resolve the uncertainties about the tolerability and treatment effect in clinical practice, it appears reasonable to assume that an improved toxicity management will result in a benefit also in the Caucasian population.

Analysis of GEJ vs GC

The lower efficacy outcome in the GEJ subgroup as compared to GC was driven by participants with distal GEJ (participants with proximal GEJ had an even more favourable outcome compared to the overall study population). Exposure to zolbetuximab (and oxaliplatin) was lower in the GEJ vs the GC subgroups and lower in the GEJ distal vs proximal participants; further suggesting that the reasons for the worse clinical outcomes in these subgroups are likely due to differences in the exposure to zolbetuximab and/or oxaliplatin. In addition, the GEJ subgroup had more and earlier dose interruptions and slightly higher early discontinuation rates compared to GC. GEJ is more frequent in Caucasian participants than in Asian (proportion of GEJ 28% vs 11%); thus, the predominance of Caucasian participants in the GEJ subgroup may have contributed to the lower efficacy of zolbetuximab in the GEJ subgroup analysis. A comparative analysis of medical condition and race, comparing Caucasian-GEJ, Asian-GEJ, Caucasian-GC and Asian-GC patients was submitted. Although this analysis should be interpreted with caution, the results suggest that it is possible that the lower efficacy outcome observed in the GEJ subgroup (Caucasian-GEJ and Asian-GEJ) could be driven by the predominance of Caucasian patients in the GEJ subgroup, instead of the medical condition itself (i.e., GEJ).

The overlap of subgroups makes it further difficult to draw conclusions on the underlying reasons. The proportion of distal GEJ appeared to have a substantial impact on the efficacy results of Caucasian. Exploratory analyses omitting the subpopulation with GEJ distal from the analysis were requested to get further insights on the relative contribution of GEJ subgroup to the worse efficacy results in Caucasian; these reported a PFS HR of 0.75 (95% CI 0.52, 1.06) and an OS HR of 0.78 (95% CI 0.55, 1.11) for Caucasian participants in SPOTLIGHT (with similar results in GLOW). In addition, Caucasian participants had less frequent prior gastrectomy than Asian (26% vs 35%), which might have also had an impact on results; for patients without gastrectomy higher incidences of (likely "on-target")

gastrointestinal toxicities were observed (see safety section), which might in turn have led to lower drug exposure and impacted efficacy outcomes in the Caucasian subgroup. Considering the small size of the subgroups, especially of distal GEJ (only 7% of study population) which leads to wide confidence intervals and inaccurate estimations and the fact that there is no biological plausibility to assume different treatment effects between proximal and distal GEJ, this issue was not further pursued since it is not expected to impact the benefit-risk in the proposed indication or warrant any restrictions of use in the Caucasian-GEJ population.

A special warning and precautions for use have been added on the mitigation measures before initiating treatment with zolbetuximab has been added to section 4.4 of the SmPC to optimize the toxicity management and improve the tolerability and treatment effect in clinical practice in both GC and GEJ (see also the discussion on clinical safety).

Other subgroup analyses:

Patients with an age beyond 65 years showed a small trend towards a lower treatment effect compared to the younger age group. Patients with older than 75 years did not appear to benefit in the SPOTLIGHT study; however, it is acknowledged that CIs are wide based on a very small sample size (n=16 and 22 for both arms) and subgroup results for patients > 75 years in the GLOW study were favourable for PFS (HR 0.4) and OS (HR 0.5). Pooled subgroup analysis across both studies (n=64; 6% of study population) resulted in a PFS HR of 0.7 (95% CI 0.45, 1.55), an OS HR of 1.03 (95% CI 0.55, 1,93) and an ORR difference of -27.4%. Overall, the sample size is too limited to draw any reliable conclusions on a possibly different treatment effect. The limited number of patients beyond age 75 years has been adequately reflected in the SmPC.

An only marginal benefit was notable for patients with mixed/other tumour type (22% of pooled study population); in the integrated efficacy analysis the PFS HR was 0.82 [95% CI 0.59, 1.13], the OS HR was 0.94 [95% CI 0.68, 1.29], and ORR difference was -0.4% (SPOTLIGHT: PFS HR 0.93, OS HR 0.99; GLOW: PFS HR 0.82, OS HR 0.95). Differences in baseline characteristics between treatment arms and chance observation might have contributed to the lower treatment effect for zolbetuximab in patients with mixed/other tumour types. Available data suggest a similar prevalence of CLDN18 expression among tumour types.

A trend towards a lower treatment effect was also notable for patients who are current smokers; however, this subgroup was relatively small (11% of pooled study population), results were not consistent across both trials and endpoints, and the point estimates were below 1 in favour of zolbetuximab with wide 95% confidence intervals.

A small trend towards a lower benefit was also observed for the subgroup of patients without prior gastrectomy (71% of pooled study population); however, PFS and OS results were still in favour of zolbetuximab over placebo: PFS HR 0.75 [0.62, 0.91], OS HR 0.82 [0.69, 0.99], ORR difference 4.3%.

Additional expert consultation

In the assessment of healthcare professionals, it was highlighted that despite recent improvements in medical approaches, new molecular targets are urgently needed, especially in patients with GEAC HER2-negative and CPS-PD-L1-negative that represent approximately 40% of all GEAC patients. Zolbetuximab offers a new opportunity in these situations.

2.6.7. Conclusions on clinical efficacy

The efficacy analyses of the two pivotal studies, SPOTLIGHT and GLOW, demonstrated statistically significant improvements in PFS and OS that can be considered clinically meaningful to support a

benefit for the addition of zolbetuximab to standard 1L chemotherapy in advanced GEJ/gastric cancer in the overall study population (which included ~50% of participants from Asian countries).

However, subgroup results of Caucasian raised concerns whether a relevant treatment effect and a favourable B/R can be expected in the European population. Results of additional analyses support the hypothesis that a lower exposure due to discontinuations/dose interruptions could be assumed as the main factor for the observed lower treatment effect in the Caucasian subgroup. Additional warnings and precautions as risk mitigation measures have been implemented in the SmPC to optimize the toxicity management and improve the tolerability in clinical practice and therefore address the potential risk of reduced exposure to zolbetuximab and/or chemotherapy (in both GC and GEJ) in this patient subgroup.

2.6.8. Clinical safety

The safety of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive is supported by safety data from the following studies and patient populations:

- Phase 3 pivotal Study 8951-CL-0301 (SPOTLIGHT)
- Phase 3 pivotal Study 8951-CL-0302 (GLOW)
- Integrated Analysis of Safety (Phase 3 Studies SPOTLIGHT + GLOW)

Table 114: Safety analysis set by pivotal study and integrated

Zolbetuximab 800/600 mg/m² + Chemotherapy	**SPOTLIGHT**		**GLOW**		**Integrated SPOTLIGHT/GLOW**	
	Zolbetuximab + mFOLFOX6	**Placebo + mFOLFOX6**	**Zolbetuximab + CAPOX**	**Placebo + CAPOX**	**Zolbetuximab + mFOLFOX6 or CAPOX**	**Placebo + mFOLFOX6 or CAPOX**
	N	N	N	N	N	N
Safety Analysis Set	279	278	254	249	533	527

Supportive safety data are further available for zolbetuximab in combination with chemotherapy from phase 2 studies (ILUSTRO and FAST), and for zolbetuximab monotherapy from phase I and phase II studies (8951-CL-0105, 8951-CL-0104, ILUSTRO, and MONO). For the identification of ADRs for zolbetuximab, an integrated analysis of safety of phase 2 (ILUSTRO and FAST) and phase 3 studies (SPOTLIGHT and GLOW), in which zolbetuximab was administered at the intended posology (800/600 mg/m^2 Q3W) in combination with chemotherapy, was performed and utilised.

Table 115: Clinical studies providing safety data for zolbetuximab combination and monotherapy

Study Identifier	Study Design	Number of Participants Treated	Dosage Regimen	Study population
8951-CL-0301 'SPOTLIGHT study'	Phase 3, multicenter, global, randomized, double-blind, placebo-controlled study	N = 565	Zolbetuximab 800/600 mg/m^2 Q3W + mFOLFOX6 Q2W Placebo Q3W + mFOLFOX6 Q2W	CLDN18.2-positive†, HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
8951-CL-0302 'GLOW study'	Phase 3, global, multicenter, randomized, double-blind, placebo-controlled study	N = 507	Zolbetuximab 800/600 mg/m^2 Q3W + CAPOX Q3W Placebo Q3W + CAPOX Q3W	CLDN18.2-positive†, HER2–negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
8951-CL-0103 'ILUSTRO study' (Cohort 2)	Phase 2, multicenter, open-label, nonrandomized study	N = 21	Cohort 2: Zolbetuximab 800/600 mg/m^2 Q3W + mFOLFOX6 Q2W	CLDN18.2-positive†, HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma
GM-IMAB-001-03 'FAST study'	Phase 2, randomized, multicenter, open-label, multiple dose efficacy and safety study	N = 246	Zolbetuximab 800/600 mg/m^2 Q3W + EOX Q3W Zolbetuximab 1000 mg/m^2 Q3W + EOX Q3W EOX Q3W	CLDN18.2-positive†, advanced adenocarcinoma of the stomach, the esophagus or the GEJ
GM-IMAB-001-02 'MONO Study'	Phase 2a, multicenter, open-label, multiple dose, uncontrolled, efficacy and safety study	N = 50	Cohorts 2 + 3: Zolbetuximab 600 mg/m^2 Q2W	CLDN18.2-positive†, metastatic, refractory or recurrent disease of advanced adenocarcinoma of the stomach or the lower esophagus proven by histology
8951-CL-0103 (ILUSTRO – Cohort 1A), 8951-CL-0104 8951-CL-0105	ILUSTRO: Phase 2, open-label, nonrandomized study 8951-CL-0104 and 8951-CL-0105: Phase 1 open-label studies	N = 57	Pooled Q3W data: Zolbetuximab 800/600 mg/m^2 Q3W	CLDN18.2-positive†, ≥ 3rd lines of metastatic or locally advanced unresectable gastric/GEJ adenocarcinoma

At the time of submission of the MAA, the pivotal phase 3 studies SPOTLIGHT and GLOW were still ongoing. Data cutoff dates were 9 September 2022 for SPOTLIGHT and 7 October 2022 for GLOW. In SPOTLIGHT, 16.8% and 15.1% of patients were still on treatment with zolbetuximab and placebo, respectively. In GLOW, 11.8% and 7.2% of patients were still on treatment with zolbetuximab and placebo, respectively.

In SPOTLIGHT, the median study follow-up time (defined as the duration from the first dosing of zolbetuximab/placebo to the date of completion of the 90-day follow-up period, date of discontinuation from the 90-day follow up period, date of death or date of CSR cutoff in case of ongoing participants) was 8.608 months in the zolbetuximab group and 8.871 months in the placebo group. In GLOW, the

median study follow-up time was 6.965 months in the zolbetuximab group and 7.162 months in the placebo group.

2.6.8.1. Patient exposure

Zolbetuximab was administered as 2-hour IV infusion at 800 mg/m² loading dose at C1D1, followed by subsequent doses of 600 mg/m² every 3 weeks. Treatment was continued until protocol-defined study treatment discontinuation criteria were met. Participants in SPOTLIGHT also received up to 12 treatments of mFOLFOX6. Participants in GLOW also received up to 8 treatments of CAPOX treatment.

Table 116: Extent of Exposure to Zolbetuximab or Placebo in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Characteristic Category/Statistic	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Duration of Zolbetuximab or Placebo (days)						
N	279	278	253	249	532	527
Mean (SD)	260.6 (242.0)	237.0 (182.1)	194.8 (191.9)	176.7 (148.4)	229.3 (221.8)	208.5 (169.5)
Median (min, max)	190.0 (1, 1246)	195.0 (1, 1016)	134.0 (1, 933)	148.0 (1, 848)	171.0 (1, 1246)	173.0 (1, 1016)
Duration of Treatment, Cumulative Category (n [%])						
≥ 1 day	279 (100.0)	278 (100.0)	253 (99.6)	249 (100.0)	-	-
> 6 weeks	239 (85.7)	261 (93.9)	198 (78.0)	214 (85.9)	-	-
> 12 weeks	206 (73.8)	227 (81.7)	170 (66.9)	179 (71.9)	-	-
> 24 weeks	166 (59.5)	165 (59.4)	112 (44.1)	114 (45.8)	-	-
> 36 weeks	112 (40.1)	102 (36.7)	66 (26.0)	57 (22.9)	-	-
> 48 weeks	78 (28.0)	59 (21.2)	45 (17.7)	32 (12.9)	-	-
> 72 weeks	41 (14.7)	25 (9.0)	28 (11.0)	11 (4.4)	-	-
Cumulative Actual Dose (mg/m²)†						
Mean (SD)	7308.702 (6486.533)	6858.815 (4778.716)	5706.338 (5109.237)	5294.084 (3855.859)	6546.676 (5920.986)	6119.502 (4432.507)
Median (min, max)	5600.000 (135.03, 36200.00)	5638.751 (798.13, 27800.00)	3832.632 (51.17, 24339.01)	4400.000 (27.94, 23000.00)	5000.000 (51.17, 36200.00)	5000.000 (27.94, 27800.00)
Relative Dose Intensity (%)‡						
Mean (SD)	92.336 (19.002)	98.474 (4.797)	96.094 (15.619)	99.591 (6.315)	94.123 (17.560)	99.002 (5.588)
Median (min, max)	100.000 (9.64, 184.18)	100.000 (63.43, 112.50)	100.000 (6.40, 146.78)	100.000 (3.49, 114.29)	100.000 (6.40, 184.18)	100.000 (3.49, 114.29)
Number of Infusions Entirely Administered¶						
N	261	278	241	248	502	526
Mean (SD)	12.6 (10.8)	11.1 (8.0)	9.6 (8.5)	8.5 (6.4)	11.1 (9.9)	9.9 (7.4)
Median (min, max)	10.0 (1, 60)	9.0 (1, 46)	7.0 (1, 40)	7.0 (1, 38)	8.0 (1, 60)	8.0 (1, 46)
Number of Infusions Not Entirely Administered¶						
N	73	1	36	5	109	6
Mean (SD)	1.8 (1.2)	1.0 (NE)	1.3 (0.5)	1.0 (0.0)	1.6 (1.0)	1.0 (0.0)
Median (min, max)	1.0 (1, 8)	1.0 (1, 1)	1.0 (1, 3)	1.0 (1, 1)	1.0 (1, 8)	1.0 (1, 1)
Infusions Not Administered, n (%)	32 (11.5)	36 (12.9)	12 (4.7)	15 (6.0)	44 (8.3)	51 (9.7)

Characteristic Category/Statistic	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Infusion Delayed, n (%)	68 (24.4)	46 (16.5)	43 (16.9)	46 (18.5)	111 (20.8)	92 (17.5)
Dose Interruptions, n (%)	166 (59.5)	15 (5.4)	108 (42.5)	10 (4.0)	274 (51.4)	25 (4.7)
Infusion Discontinued, n (%)	49 (17.6)	0	27 (10.6)	3 (1.2)	76 (14.3)	3 (0.6)

Table 117: Duration of Exposure to Chemotherapy Components (Phase 3 Studies)

Characteristic Category/Statistic	SPOTLIGHT		GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)
Duration of Oxaliplatin (days)			**Duration of Oxaliplatin (days)**	
N	274	278	250	249
Mean (SD)	131.3 (56.5)	130.0 (51.7)	110.2 (61.9)	110.4 (58.9)
Median (min, max)	150.0 (1, 267)	148.0 (1, 253)	123.5 (1, 240)	118.0 (1, 223)
Duration of Leucovorin (days)			**Duration of Capecitabine (days)**	
N	178	186	248	249
Mean (SD)	234.2 (233.2)	204.0 (176.9)	189.6 (166.9)	170.7 (134.7)
Median (min, max)	180.5 (1, 1254)	169.0 (1,1030)	141.5 (1, 757)	141.0 (1, 862)
Duration of Levo-Folinic Acid (days)			**-**	
N	127	112	-	-
Mean (SD)	245.5 (214.5)	218.5 (179.0)	-	-
Median (min, max)	183.0 (1, 911)	178.5 (1, 919)	-	-
Duration of Fluorouracil (days)			**-**	
N	273	278	-	-
Mean (SD)	267.0 (225.4)	225.9 (175.2)	-	-
Median (min, max)	198.0 (2, 1256)	178.0 (3, 1032)	-	-
mFOLFOX6 (24 weeks) Treatment Completed			**CAPOX (24 weeks) Treatment Completed**	
n	103 (36.9%)	99 (35.6%)	70 (27.6%)	69 (27.7%)

2.6.8.2. Adverse events

Safety was evaluated using AEs, vital signs, ECGs, physical exams, ECOG performance status and laboratory assessments. Severity of AEs and laboratory abnormalities were assessed based on NCI-CTCAE v4.03. MedDRA version 25.0 was used to code AEs across the zolbetuximab program for the ISS. TEAEs are defined as any AE observed after starting administration of the study treatment and within 30 days after the last dose of study treatment.

Participants with at least 1 TEAE could be counted in both categories, 'zolbetuximab- or placebo-related TEAEs' and 'any chemotherapy-related TEAEs', depending on the investigator's causality assessment of the respective TEAEs: The investigator could attribute TEAEs specifically to zolbetuximab/placebo, specifically to chemotherapy or to both zolbetuximab/placebo and chemotherapy.

Overview of treatment-emergent adverse events

Table 118: Overview of TEAEs in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
Category, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any TEAE	**278 (99.6)**	**277 (99.6)**	**251 (98.8)**	**244 (98.0)**	**529 (99.2)**	**521 (98.9)**
Drug-related †	277 (99.3)	268 (96.4)	246 (96.9)	234 (94.0)	523 (98.1)	502 (95.3)
Zolbetuximab or placebo-related †	255 (91.4)	216 (77.7)	231 (90.9)	168 (67.5)	486 (91.2)	384 (72.9)
Any chemotherapy-related	264 (94.6)	268 (96.4)	235 (92.5)	233 (93.6)	499 (93.6)	501 (95.1)
Serious TEAE‡	**125 (44.8)**	**121 (43.5)**	**120 (47.2)**	**124 (49.8)**	**245 (46.0)**	**245 (46.5)**
Drug-related †‡	66 (23.7)	41 (14.7)	68 (26.8)	56 (22.5)	134 (25.1)	97 (18.4)
Zolbetuximab or placebo-related †‡	47 (16.8)	28 (10.1)	50 (19.7)	39 (15.7)	97 (18.2)	67 (12.7)
Any chemotherapy-related	55 (19.7)	35 (12.6)	59 (23.2)	54 (21.7)	114 (21.4)	89 (16.9)
TEAE Leading to Death	**22 (7.9)**	**24 (8.6)**	**27 (10.6)**	**32 (12.9)**	**49 (9.2)**	**56 (10.6)**
Drug-related †	5 (1.8)	4 (1.4)	6 (2.4)	7 (2.8)	11 (2.1)	11 (2.1)
Zolbetuximab or placebo-related †	4 (1.4)	3 (1.1)	4 (1.6)	3 (1.2)	8 (1.5)	6 (1.1)
Any chemotherapy-related †	4 (1.4)	4 (1.4)	6 (2.4)	7 (2.8)	10 (1.9)	11 (2.1)
TEAE Leading to Permanent Discontinuation of Any Study Drug§	**120 (43.0)**	**106 (38.1)**	**79 (31.1)**	**63 (25.3)**	**199 (37.3)**	**169 (32.1)**
TEAE leading to permanent discontinuation of zolbetuximab or placebo	55 (19.7)	30 (10.8)	51 (20.1)	36 (14.5)	106 (19.9)	66 (12.5)
Drug-related TEAE Leading to Permanent Discontinuation of Any Study Drug†§	**106 (38.0)**	**82 (29.5)**	**55 (21.7)**	**39 (15.7)**	**161 (30.2)**	**121 (23.0)**
Drug-related TEAE leading to permanent discontinuation of zolbetuximab or placebo†	38 (13.6)	6 (2.2)	18 (7.1)	11 (4.4)	56 (10.5)	17 (3.2)
Any chemotherapy-related TEAE leading to permanent discontinuation of any chemotherapy†§	86 (30.8)	80 (28.8)	44 (17.3)	37 (14.9)	130 (24.4)	117 (22.2)
TEAE Leading to Dose Interruption of Any Study Drug§	**228 (81.7)**	**156 (56.1)**	**181 (71.3)**	**128 (51.4)**	**409 (76.7)**	**284 (53.9)**
TEAE leading to dose interruption of zolbetuximab or placebo	208 (74.6)	111 (39.9)	140 (55.1)	71 (28.5)	348 (65.3)	182 (34.5)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Drug-related TEAE Leading to Dose Interruption of Any Study Drug†§	**215 (77.1)**	**128 (46.0)**	**167 (65.7)**	**108 (43.4)**	**382 (71.7)**	**236 (44.8)**
Drug-related TEAE leading to dose interruption of zolbetuximab or placebo†	171 (61.3)	56 (20.1)	113 (44.5)	39 (15.7)	284 (53.3)	95 (18.0)
Any chemotherapy-related TEAE leading to dose interruption of any chemotherapy†§	119 (42.7)	109 (39.2)	109 (42.9)	101 (40.6)	228 (42.8)	210 (39.8)
NCI-CTCAE Grade TEAE¶ ≥ 3	**242 (86.7)**	**216 (77.7)**	**185 (72.8)**	**174 (69.9)**	**427 (80.1)**	**390 (74.0)**
Drug-related †¶	219 (78.5)	172 (61.9)	144 (56.7)	115 (46.2)	363 (68.1)	287 (54.5)
Zolbetuximab or Placebo-related †¶	149 (53.4)	91 (32.7)	98 (38.6)	63 (25.3)	247 (46.3)	154 (29.2)
Any chemotherapy-†¶	199 (71.3)	168 (60.4)	130 (51.2)	112 (45.0)	329 (61.7)	280 (53.1)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Most common treatment-emergent adverse events

Table 119: Common (Occurring in ≥ 10% of Participants in Any Treatment Group) TEAEs in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any TEAE	**278 (99.6)**	**277 (99.6)**	**251 (98.8)**	**244 (98.0)**	**529 (99.2)**	**521 (98.9)**
Blood and Lymphatic System Disorders	**166 (59.5)**	**167 (60.1)**	**131 (51.6)**	**126 (50.6)**	**297 (55.7)**	**293 (55.6)**
Anemia	100 (35.8)	104 (37.4)	90 (35.4)	91 (36.5)	190 (35.6)	195 (37.0)
Neutropenia	102 (36.6)	94 (33.8)	50 (19.7)	35 (14.1)	152 (28.5)	129 (24.5)
Thrombocytopenia	28 (10.0)	45 (16.2)	28 (11.0)	31 (12.4)	56 (10.5)	76 (14.4)
Gastrointestinal Disorders	**264 (94.6)**	**250 (89.9)**	**234 (92.1)**	**199 (79.9)**	**498 (93.4)**	**449 (85.2)**
Nausea	230 (82.4)	169 (60.8)	174 (68.5)	125 (50.2)	404 (75.8)	294 (55.8)
Vomiting	188 (67.4)	99 (35.6)	168 (66.1)	77 (30.9)	356 (66.8)	176 (33.4)
Diarrhoea	110 (39.4)	122 (43.9)	80 (31.5)	86 (34.5)	190 (35.6)	208 (39.5)
Constipation	99 (35.5)	112 (40.3)	39 (15.4)	52 (20.9)	138 (25.9)	164 (31.1)
Abdominal pain	67 (24.0)	82 (29.5)	40 (15.7)	54 (21.7)	107 (20.1)	136 (25.8)
Abdominal pain upper	47 (16.8)	32 (11.5)	23 (9.1)	13 (5.2)	70 (13.1)	45 (8.5)
Stomatitis	58 (20.8)	57 (20.5)	8 (3.1)	7 (2.8)	66 (12.4)	64 (12.1)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any TEAE	**278 (99.6)**	**277 (99.6)**	**251 (98.8)**	**244 (98.0)**	**529 (99.2)**	**521 (98.9)**
General Disorders and Administration Site Conditions	**207 (74.2)**	**202 (72.7)**	**139 (54.7)**	**125 (50.2)**	**346 (64.9)**	**327 (62.0)**
Fatigue	78 (28.0)	91 (32.7)	34 (13.4)	42 (16.9)	112 (21.0)	133 (25.2)
Asthenia	74 (26.5)	64 (23.0)	33 (13.0)	32 (12.9)	107 (20.1)	96 (18.2)
Pyrexia	54 (19.4)	48 (17.3)	34 (13.4)	23 (9.2)	88 (16.5)	71 (13.5)
Oedema peripheral	49 (17.6)	26 (9.4)	26 (10.2)	6 (2.4)	75 (14.1)	32 (6.1)
Malaise	21 (7.5)	9 (3.2)	31 (12.2)	22 (8.8)	52 (9.8)	31 (5.9)
Investigations	**182 (65.2)**	**171 (61.5)**	**153 (60.2)**	**150 (60.2)**	**335 (62.9)**	**321 (60.9)**
Neutrophil count decreased	95 (34.1)	91 (32.7)	70 (27.6)	59 (23.7)	165 (31.0)	150 (28.5)
Aspartate aminotransferase increased	49 (17.6)	44 (15.8)	63 (24.8)	72 (28.9)	112 (21.0)	116 (22.0)
Weight decreased	55 (19.7)	54 (19.4)	50 (19.7)	25 (10.0)	105 (19.7)	79 (15.0)
Platelet count decreased	40 (14.3)	49 (17.6)	61 (24.0)	60 (24.1)	101 (18.9)	109 (20.7)
White blood cell count decreased	50 (17.9)	46 (16.5)	51 (20.1)	39 (15.7)	101 (18.9)	85 (16.1)
Alanine aminotransferase increased	34 (12.2)	47 (16.9)	48 (18.9)	52 (20.9)	82 (15.4)	99 (18.8)
Metabolism and Nutrition Disorders	**189 (67.7)**	**159 (57.2)**	**154 (60.6)**	**138 (55.4)**	**343 (64.4)**	**297 (56.4)**
Decreased appetite	131 (47.0)	93 (33.5)	105 (41.3)	84 (33.7)	236 (44.3)	177 (33.6)
Hypoalbuminaemia	43 (15.4)	17 (6.1)	57 (22.4)	35 (14.1)	100 (18.8)	52 (9.9)
Hypokalaemia	50 (17.9)	41 (14.7)	36 (14.2)	36 (14.5)	86 (16.1)	77 (14.6)
Hypocalcaemia	30 (10.8)	9 (3.2)	13 (5.1)	12 (4.8)	43 (8.1)	21 (4.0)
Musculoskeletal and Connective Tissue Disorders	**81 (29.0)**	**86 (30.9)**	**31 (12.2)**	**52 (20.9)**	**112 (21.0)**	**138 (26.2)**
Back pain	34 (12.2)	30 (10.8)	8 (3.1)	20 (8.0)	42 (7.9)	50 (9.5)
Nervous System Disorders	**209 (74.9)**	**208 (74.8)**	**138 (54.3)**	**143 (57.4)**	**347 (65.1)**	**351 (66.6)**
Peripheral sensory neuropathy	106 (38.0)	118 (42.4)	56 (22.0)	56 (22.5)	162 (30.4)	174 (33.0)
Dysgeusia	41 (14.7)	40 (14.4)	18 (7.1)	12 (4.8)	59 (11.1)	52 (9.9)
Paraesthesia	44 (15.8)	46 (16.5)	13 (5.1)	11 (4.4)	57 (10.7)	57 (10.8)
Dizziness	36 (12.9)	27 (9.7)	14 (5.5)	11 (4.4)	50 (9.4)	38 (7.2)
Hypoaesthesia	11 (3.9)	11 (4.0)	30 (11.8)	30 (12.0)	41 (7.7)	41 (7.8)
Headache	31 (11.1)	35 (12.6)	8 (3.1)	8 (3.2)	39 (7.3)	43 (8.2)
Psychiatric Disorders	**46 (16.5)**	**44 (15.8)**	**33 (13.0)**	**25 (10.0)**	**79 (14.8)**	**69 (13.1)**
Insomnia	29 (10.4)	25 (9.0)	27 (10.6)	16 (6.4)	56 (10.5)	41 (7.8)
Respiratory, Thoracic and Mediastinal Disorders	**106 (38.0)**	**112 (40.3)**	**52 (20.5)**	**61 (24.5)**	**158 (29.6)**	**173 (32.8)**
Cough	28 (10.0)	28 (10.1)	11 (4.3)	14 (5.6)	39 (7.3)	42 (8.0)
Dyspnoea	20 (7.2)	32 (11.5)	15 (5.9)	13 (5.2)	35 (6.6)	45 (8.5)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any TEAE	**278 (99.6)**	**277 (99.6)**	**251 (98.8)**	**244 (98.0)**	**529 (99.2)**	**521 (98.9)**
Skin and Subcutaneous Tissue Disorders	**125 (44.8)**	**113 (40.6)**	**78 (30.7)**	**74 (29.7)**	**203 (38.1)**	**187 (35.5)**
Palmar-plantar erythrodysaesthesia syndrome	24 (8.6)	19 (6.8)	41 (16.1)	49 (19.7)	65 (12.2)	68 (12.9)
Vascular Disorders	**77 (27.6)**	**65 (23.4)**	**53 (20.9)**	**29 (11.6)**	**130 (24.4)**	**94 (17.8)**
Hypertension	31 (11.1)	22 (7.9)	15 (5.9)	7 (2.8)	46 (8.6)	29 (5.5)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.
Source: Table 7 SCS

Summaries of overall TEAEs, SAEs, and grade ≥ 3 TEAEs related to any drug were provided (data not shown). The safety profile of any drug-related TEAEs comparing the zolbetuximab vs. the comparator arms resembles those profiles presented for all-cause TEAEs and zolbetuximab- or placebo-related TEAEs.

A tendency towards an increased occurrence of vascular disorders is apparent in the combined phase 3 zolbetuximab group as compared to the combined phase 3 control group (24.4% vs. 17.8%), of which the PT of hypertension was reported as most common TEAE. For evaluation of the identified signal of increased incidences of thrombotic events in patients treated with zolbetuximab, the Applicant provided a pooled summary of all TEAEs, TEAEs ≥ Grade 3 and serious TEAEs of thrombosis/embolism by PT based on integrated data from the phase 2 and phase 3 studies, see tables below.

Table 120: TEAEs of Interest: Thrombosis/Embolism by Preferred Term (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated FAST/ILUSTRO/SPOTLIGHT/GLOW	
	Zolbetuximab + EOX/mFOLFOX6/CAPOX (n = 631)†	EOX or Placebo + mFOLFOX6/CAPOX (n = 611)‡
Overall	**66 (10.5)**	**43 (7.0)**
Pulmonary embolism	25 (4.0)	25 (4.1)
Deep vein thrombosis	22 (3.5)	12 (2.0)
Venous thrombosis	6 (1.0)	2 (0.3)
Superficial vein thrombosis	4 (0.6)	2 (0.3)
Venous thrombosis limb	4 (0.6)	1 (0.2)
Embolism venous	3 (0.5)	0
Jugular vein thrombosis	3 (0.5)	4 (0.7)
Vena cava thrombosis	3 (0.5)	0
Axillary vein thrombosis	1 (0.2)	0
Pelvic venous thrombosis	1 (0.2)	0
Hepatic vein thrombosis	0	1 (0.2)

Source: Table EMA129-1

Table 121: TEAEs of Interest with NCI-CTCAE ≥3: Thrombosis/Embolism by Preferred Term (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated FAST/ILUSTRO/SPOTLIGHT/GLOW	
	Zolbetuximab + EOX/mFOLFOX6/CAPOX (n = 631)†	EOX or Placebo + mFOLFOX6/CAPOX (n = 611)‡
Overall	**25 (4.0)**	**18 (2.9)**
Pulmonary embolism	14 (2.2)	17 (2.8)
Deep vein thrombosis	6 (1.0)	2 (0.3)
Vena cava thrombosis	2 (0.3)	0
Venous thrombosis	2 (0.3)	0
Embolism venous	1 (0.2)	0
Jugular vein thrombosis	1 (0.2)	0
Superficial vein thrombosis	1 (0.2)	0

Source: Table EMA129-2

Table 122: Serious TEAEs of Interest: Thrombosis/Embolism by Preferred Term (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated FAST/ILUSTRO/SPOTLIGHT/GLOW	
	Zolbetuximab + EOX/mFOLFOX6/CAPOX (n = 631)†	EOX or Placebo + mFOLFOX6/CAPOX (n = 611)‡
Overall	**19 (3.0)**	**16 (2.6)**
Pulmonary embolism	9 (1.4)	14 (2.3)
Deep vein thrombosis	5 (0.8)	1 (0.2)
Embolism venous	2 (0.3)	0
Venous thrombosis	2 (0.3)	1 (0.2)
Jugular vein thrombosis	1 (0.2)	0
Vena cava thrombosis	1 (0.2)	0

Source: Table EMA129-3

Most common TEAEs related to zolbetuximab or placebo

In the SCS, all-cause TEAEs and zolbetuximab- or placebo-related TEAEs have been presented. No summary of TEAE related to any study drug was provided.

Table 123: Zolbetuximab or Placebo-related TEAEs Occurring in ≥ 5% of Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Zolbetuximab or Placebo-related TEAE	**255 (91.4)**	**216 (77.7)**	**231 (90.9)**	**168 (67.5)**	**486 (91.2)**	**384 (72.9)**
Blood and Lymphatic System Disorders	**83 (29.7)**	**81 (29.1)**	**66 (26.0)**	**60 (24.1)**	**149 (28.0)**	**141 (26.8)**
Anemia	40 (14.3)	48 (17.3)	40 (15.7)	39 (15.7)	80 (15.0)	87 (16.5)
Neutropenia	54 (19.4)	44 (15.8)	22 (8.7)	17 (6.8)	76 (14.3)	61 (11.6)
Thrombocytopenia	14 (5.0)	24 (8.6)	16 (6.3)	15 (6.0)	30 (5.6)	39 (7.4)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Gastrointestinal Disorders	**226 (81.0)**	**148 (53.2)**	**198 (78.0)**	**114 (45.8)**	**424 (79.5)**	**262 (49.7)**
Nausea	192 (68.8)	103 (37.1)	154 (60.6)	87 (34.9)	346 (64.9)	190 (36.1)
Vomiting	161 (57.7)	42 (15.1)	154 (60.6)	45 (18.1)	315 (59.1)	87 (16.5)
Diarrhoea	51 (18.3)	47 (16.9)	40 (15.7)	28 (11.2)	91 (17.1)	75 (14.2)
Abdominal pain	28 (10.0)	14 (5.0)	14 (5.5)	13 (5.2)	42 (7.9)	27 (5.1)
Constipation	28 (10.0)	26 (9.4)	13 (5.1)	9 (3.6)	41 (7.7)	35 (6.6)
Abdominal pain upper	20 (7.2)	2 (0.7)	9 (3.5)	4 (1.6)	29 (5.4)	6 (1.1)
Dyspepsia	17 (6.1)	8 (2.9)	5 (2.0)	1 (0.4)	22 (4.1)	9 (1.7)
Stomatitis	18 (6.5)	18 (6.5)	1 (0.4)	3 (1.2)	19 (3.6)	21 (4.0)
General Disorders and Administration Site Conditions	**120 (43.0)**	**100 (36.0)**	**87 (34.3)**	**69 (27.7)**	**207 (38.8)**	**169 (32.1)**
Fatigue	49 (17.6)	58 (20.9)	19 (7.5)	27 (10.8)	68 (12.8)	85 (16.1)
Asthenia	37 (13.3)	35 (12.6)	19 (7.5)	16 (6.4)	56 (10.5)	51 (9.7)
Malaise	14 (5.0)	4 (1.4)	28 (11.0)	17 (6.8)	42 (7.9)	21 (4.0)
Pyrexia	10 (3.6)	8 (2.9)	17 (6.7)	5 (2.0)	27 (5.1)	13 (2.5)
Oedema peripheral	15 (5.4)	4 (1.4)	7 (2.8)	0	22 (4.1)	4 (0.8)
Investigations	**86 (30.8)**	**85 (30.6)**	**83 (32.7)**	**80 (32.1)**	**169 (31.7)**	**165 (31.3)**
Neutrophil count decreased	43 (15.4)	49 (17.6)	41 (16.1)	25 (10.0)	84 (15.8)	74 (14.0)
Aspartate aminotransferase increased	23 (8.2)	23 (8.3)	37 (14.6)	41 (16.5)	60 (11.3)	64 (12.1)
White blood cell count decreased	26 (9.3)	25 (9.0)	27 (10.6)	18 (7.2)	53 (9.9)	43 (8.2)
Platelet count decreased	21 (7.5)	23 (8.3)	27 (10.6)	32 (12.9)	48 (9.0)	55 (10.4)
Alanine aminotransferase increased	16 (5.7)	21 (7.6)	31 (12.2)	27 (10.8)	47 (8.8)	48 (9.1)
Weight decreased	18 (6.5)	10 (3.6)	19 (7.5)	10 (4.0)	37 (6.9)	20 (3.8)
Metabolism and Nutrition Disorders	**85 (30.5)**	**71 (25.5)**	**88 (34.6)**	**72 (28.9)**	**173 (32.5)**	**143 (27.1)**
Decreased appetite	68 (24.4)	53 (19.1)	73 (28.7)	52 (20.9)	141 (26.5)	105 (19.9)
Hypoalbuminaemia	12 (4.3)	3 (1.1)	15 (5.9)	13 (5.2)	27 (5.1)	16 (3.0)
Hypokalaemia	15 (5.4)	7 (2.5)	7 (2.8)	12 (4.8)	22 (4.1)	19 (3.6)
Nervous System Disorders	**64 (22.9)**	**45 (16.2)**	**41 (16.1)**	**31 (12.4)**	**105 (19.7)**	**76 (14.4)**
Dysgeusia	18 (6.5)	15 (5.4)	7 (2.8)	3 (1.2)	25 (4.7)	18 (3.4)
Dizziness	14 (5.0)	7 (2.5)	8 (3.1)	3 (1.2)	22 (4.1)	10 (1.9)
Vascular Disorders	**37 (13.3)**	**13 (4.7)**	**23 (9.1)**	**9 (3.6)**	**60 (11.3)**	**22 (4.2)**
Hypertension	23 (8.2)	4 (1.4)	13 (5.1)	1 (0.4)	36 (6.8)	5 (0.9)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Treatment-emergent adverse events grade ≥ 3

Table 124: NCI-CTCAE Grade ≥ 3 TEAEs (All-cause) Occurring in ≥ 5% of Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Overall	**242 (86.7)**	**216 (77.7)**	**185 (72.8)**	**174 (69.9)**	**427 (80.1)**	**390 (74.0)**
Neutropenia	79 (28.3)	65 (23.4)	18 (7.1)	7 (2.8)	97 (18.2)	72 (13.7)
Neutrophil count decreased	69 (24.7)	69 (24.8)	26 (10.2)	24 (9.6)	95 (17.8)	93 (17.6)
Vomiting	45 (16.1)	16 (5.8)	31 (12.2)	9 (3.6)	76 (14.3)	25 (4.7)
Nausea	45 (16.1)	18 (6.5)	22 (8.7)	6 (2.4)	67 (12.6)	24 (4.6)
Anaemia	24 (8.6)	26 (9.4)	27 (10.6)	28 (11.2)	51 (9.6)	54 (10.2)
Decreased appetite	16 (5.7)	9 (3.2)	17 (6.7)	4 (1.6)	33 (6.2)	13 (2.5)
Hypokalaemia	16 (5.7)	10 (3.6)	14 (5.5)	16 (6.4)	30 (5.6)	26 (4.9)
Asthenia	20 (7.2)	7 (2.5)	7 (2.8)	3 (1.2)	27 (5.1)	10 (1.9)
Diarrhoea	12 (4.3)	9 (3.2)	15 (5.9)	18 (7.2)	27 (5.1)	27 (5.1)
Fatigue	17 (6.1)	14 (5.0)	7 (2.8)	9 (3.6)	24 (4.5)	23 (4.4)
Platelet count decreased	3 (1.1)	6 (2.2)	19 (7.5)	20 (8.0)	22 (4.1)	26 (4.9)
Hypertension	15 (5.4)	10 (3.6)	6 (2.4)	3 (1.2)	21 (3.9)	13 (2.5)
Malignant neoplasm progression	10 (3.6)	12 (4.3)	9 (3.5)	13 (5.2)	19 (3.6)	25 (4.7)
White blood cell count decreased	8 (2.9)	16 (5.8)	5 (2.0)	9 (3.6)	13 (2.4)	25 (4.7)
Peripheral sensory neuropathy	11 (3.9)	15 (5.4)	1 (0.4)	6 (2.4)	12 (2.3)	21 (4.0)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Source: SCS Table 8, modified

Treatment-emergent adverse events grade ≥ 3 related to zolbetuximab or placebo

Table 125: NCI-CTCAE Grade ≥ 3 TEAEs Related to Zolbetuximab or Placebo Occurring in ≥ 5% of Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Overall	**149 (53.4)**	**91 (32.7)**	**98 (38.6)**	**63 (25.3)**	**247 (46.3)**	**154 (29.2)**
Neutropenia	38 (13.6)	31 (11.2)	8 (3.1)	4 (1.6)	46 (8.6)	35 (6.6)
Neutrophil count decreased	31 (11.1)	37 (13.3)	14 (5.5)	8 (3.2)	45 (8.4)	45 (8.5)
Vomiting	36 (12.9)	4 (1.4)	27 (10.6)	5 (2.0)	63 (11.8)	9 (1.7)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Overall	**149 (53.4)**	**91 (32.7)**	**98 (38.6)**	**63 (25.3)**	**247 (46.3)**	**154 (29.2)**
Neutropenia	38 (13.6)	31 (11.2)	8 (3.1)	4 (1.6)	46 (8.6)	35 (6.6)
Nausea	35 (12.5)	6 (2.2)	18 (7.1)	4 (1.6)	53 (9.9)	10 (1.9)
Anaemia	11 (3.9)	9 (3.2)	10 (3.9)	11 (4.4)	21 (3.9)	20 (3.8)
Decreased appetite	9 (3.2)	4 (1.4)	14 (5.5)	1 (0.4)	23 (4.3)	5 (0.9)
Hypokalaemia	2 (0.7)	2 (0.7)	4 (1.6)	6 (2.4)	6 (1.1)	8 (1.5)
Asthenia	6 (2.2)	3 (1.1)	4 (1.6)	1 (0.4)	10 (1.9)	4 (0.8)
Diarrhoea	3 (1.1)	0	4 (1.6)	6 (2.4)	7 (1.3)	6 (1.1)
Fatigue	8 (2.9)	6 (2.2)	2 (0.8)	3 (1.2)	10 (1.9)	9 (1.7)
Platelet count decreased	1 (0.4)	5 (1.8)	10 (3.9)	13 (5.2)	11 (2.1)	18 (3.4)
Hypertension	9 (3.2)	2 (0.7)	4 (1.6)	0	13 (2.4)	2 (0.4)
Malignant neoplasm progression	0	0	1 (0.4)	0	1 (0.2)	0
White blood cell count decreased	6 (2.2)	9 (3.2)	2 (0.8)	3 (1.2)	8 (1.5)	12 (2.3)
Peripheral sensory neuropathy	0	1 (0.4)	0	0	0	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.
Source: SCS Table 8, modified

2.6.8.3. Serious adverse events, deaths, and other significant events

Serious treatment-emergent adverse events

Table 126: Serious TEAEs Occurring in ≥ 1% of Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Serious TEAE	**125 (44.8)**	**121 (43.5)**	**120 (47.2)**	**124 (49.8)**	**245 (46.0)**	**245 (46.5)**
Blood and Lymphatic System Disorders	**17 (6.1)**	**9 (3.2)**	**12 (4.7)**	**15 (6.0)**	**29 (5.4)**	**24 (4.6)**
Anaemia	5 (1.8)	4 (1.4)	5 (2.0)	6 (2.4)	10 (1.9)	10 (1.9)
Neutropenia	6 (2.2)	3 (1.1)	4 (1.6)	2 (0.8)	10 (1.9)	5 (0.9)
Febrile neutropenia	8 (2.9)	1 (0.4)	0	3 (1.2)	8 (1.5)	4 (0.8)
Thrombocytopenia	1 (0.4)	0	3 (1.2)	2 (0.8)	4 (0.8)	2 (0.4)
Gastrointestinal Disorders	**52 (18.6)**	**42 (15.1)**	**57 (22.4)**	**50 (20.1)**	**109 (20.5)**	**92 (17.5)**
Vomiting	23 (8.2)	13 (4.7)	15 (5.9)	11 (4.4)	38 (7.1)	24 (4.6)
Nausea	19 (6.8)	11 (4.0)	11 (4.3)	6 (2.4)	30 (5.6)	17 (3.2)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Diarrhoea	8 (2.9)	4 (1.4)	7 (2.8)	10 (4.0)	15 (2.8)	14 (2.7)
Intestinal obstruction	7 (2.5)	3 (1.1)	3 (1.2)	1 (0.4)	10 (1.9)	4 (0.8)
Upper gastrointestinal haemorrhage	3 (1.1)	0	7 (2.8)	4 (1.6)	10 (1.9)	4 (0.8)
Abdominal pain	5 (1.8)	9 (3.2)	3 (1.2)	6 (2.4)	8 (1.5)	15 (2.8)
General Disorders and Administration Site Conditions	**24 (8.6)**	**22 (7.9)**	**18 (7.1)**	**13 (5.2)**	**42 (7.9)**	**35 (6.6)**
Pyrexia	7 (2.5)	6 (2.2)	5 (2.0)	2 (0.8)	12 (2.3)	8 (1.5)
Asthenia	5 (1.8)	3 (1.1)	2 (0.8)	1 (0.4)	7 (1.3)	4 (0.8)
Fatigue	4 (1.4)	3 (1.1)	3 (1.2)	3 (1.2)	7 (1.3)	6 (1.1)
Hepatobiliary Disorders	**8 (2.9)**	**13 (4.7)**	**9 (3.5)**	**7 (2.8)**	**17 (3.2)**	**20 (3.8)**
Hepatic function abnormal	1 (0.4)	3 (1.1)	2 (0.8)	0	3 (0.6)	3 (0.6)
Cholecystitis	1 (0.4)	3 (1.1)	1 (0.4)	2 (0.8)	2 (0.4)	5 (0.9)
Infections and Infestations	**29 (10.4)**	**23 (8.3)**	**25 (9.8)**	**21 (8.4)**	**54 (10.1)**	**44 (8.3)**
Pneumonia	6 (2.2)	8 (2.9)	6 (2.4)	5 (2.0)	12 (2.3)	13 (2.5)
Sepsis	5 (1.8)	1 (0.4)	1 (0.4)	2 (0.8)	6 (1.1)	3 (0.6)
COVID-19	0	2 (0.7)	3 (1.2)	3 (1.2)	3 (0.6)	5 (0.9)
Investigations	**6 (2.2)**	**9 (3.2)**	**13 (5.1)**	**10 (4.0)**	**19 (3.6)**	**19 (3.6)**
Platelet count decreased	0	0	8 (3.1)	6 (2.4)	8 (1.5)	6 (1.1)
Neutrophil count decreased	1 (0.4)	4 (1.4)	1 (0.4)	1 (0.4)	2 (0.4)	5 (0.9)
Metabolism and Nutrition Disorders	**13 (4.7)**	**9 (3.2)**	**18 (7.1)**	**15 (6.0)**	**31 (5.8)**	**24 (4.6)**
Decreased appetite	1 (0.4)	2 (0.7)	10 (3.9)	3 (1.2)	11 (2.1)	5 (0.9)
Hypokalaemia	5 (1.8)	2 (0.7)	6 (2.4)	6 (2.4)	11 (2.1)	8 (1.5)
Musculoskeletal and Connective Tissue Disorders	**2 (0.7)**	**0**	**1 (0.4)**	**6 (2.4)**	**3 (0.6)**	**6 (1.1)**
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**14 (5.0)**	**17 (6.1)**	**10 (3.9)**	**17 (6.8)**	**24 (4.5)**	**34 (6.5)**
Malignant neoplasm progression	10 (3.6)	12 (4.3)	9 (3.5)	13 (5.2)	19 (3.6)	25 (4.7)
Nervous System Disorders	**10 (3.6)**	**13 (4.7)**	**7 (2.8)**	**3 (1.2)**	**17 (3.2)**	**16 (3.0)**
Renal and Urinary Disorders	**6 (2.2)**	**6 (2.2)**	**7 (2.8)**	**8 (3.2)**	**13 (2.4)**	**14 (2.7)**
Acute kidney injury	0	2 (0.7)	4 (1.6)	1 (0.4)	4 (0.8)	3 (0.6)
Respiratory, Thoracic and Mediastinal Disorders	**14 (5.0)**	**15 (5.4)**	**9 (3.5)**	**22 (8.8)**	**23 (4.3)**	**37 (7.0)**
Pulmonary embolism	6 (2.2)	4 (1.4)	2 (0.8)	8 (3.2)	8 (1.5)	12 (2.3)
Respiratory failure	3 (1.1)	0	1 (0.4)	2 (0.8)	4 (0.8)	2 (0.4)
Dyspnoea	1 (0.4)	5 (1.8)	2 (0.8)	5 (2.0)	3 (0.6)	10 (1.9)
Pleural effusion	2 (0.7)	3 (1.1)	1 (0.4)	7 (2.8)	3 (0.6)	10 (1.9)
Vascular Disorders	**9 (3.2)**	**5 (1.8)**	**6 (2.4)**	**1 (0.4)**	**15 (2.8)**	**6 (1.1)**

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Hypotension	1 (0.4)	1 (0.4)	4 (1.6)	0	5 (0.9)	1 (0.2)
Deep vein thrombosis	4 (1.4)	1 (0.4)	0	0	4 (0.8)	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.
Source: Table 11 SCS, excerpt and modified

Serious treatment-emergent adverse events related to zolbetuximab and placebo

Table 127: Zolbetuximab- or Placebo-related Serious TEAEs Occurring in ≥ 1% of Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Serious TEAE	**47 (16.8)**	**28 (10.1)**	**50 (19.7)**	**39 (15.7)**	**97 (18.2)**	**67 (12.7)**
Blood and Lymphatic System Disorders	**9 (3.2)**	**4 (1.4)**	**2 (0.8)**	**4 (1.6)**	**11 (2.1)**	**8 (1.5)**
Anaemia	2 (0.7)	1 (0.4)	1 (0.4)	3 (1.2)	3 (0.6)	4 (0.8)
Neutropenia	3 (1.1)	2 (0.7)	1 (0.4)	1 (0.4)	4 (0.8)	3 (0.6)
Febrile neutropenia	4 (1.4)	1 (0.4)	0	0	4 (0.8)	1 (0.2)
Gastrointestinal Disorders	**23 (8.2)**	**9 (3.2)**	**27 (10.6)**	**17 (6.8)**	**50 (9.4)**	**26 (4.9)**
Vomiting	15 (5.4)	3 (1.1)	12 (4.7)	3 (1.2)	27 (5.1)	6 (1.1)
Nausea	13 (4.7)	2 (0.7)	9 (3.5)	4 (1.6)	22 (4.1)	6 (1.1)
Diarrhoea	3 (1.1)	0	2 (0.8)	4 (1.6)	5 (0.9)	4 (0.8)
Intestinal obstruction	1 (0.4)	0	0	0	1 (0.2)	0
Upper gastrointestinal haemorrhage	2 (0.7)	0	4 (1.6)	1 (0.4)	6 (1.1)	1 (0.2)
Abdominal pain	1 (0.4)	2 (0.7)	0	0	1 (0.2)	2 (0.4)
General Disorders and Administration Site Conditions	**5 (1.8)**	**5 (1.8)**	**7 (2.8)**	**4 (1.6)**	**12 (2.3)**	**9 (1.7)**
Pyrexia	0	0	0	1 (0.4)	0	1 (0.2)
Asthenia	1 (0.4)	0	2 (0.8)	0	3 (0.6)	0
Fatigue	2 (0.7)	3 (1.1)	2 (0.8)	1 (0.4)	4 (0.8)	4 (0.8)
Hepatobiliary Disorders	**0**	**3 (1.1)**	**4 (1.6)**	**1 (0.4)**	**4 (0.8)**	**4 (0.8)**
Hepatic function abnormal	**0**	2 (0.7)	1 (0.4)	0	1 (0.2)	2 (0.4)
Cholecystitis	**0**	0	0	1 (0.4)	0	1 (0.2)
Infections and Infestations	**4 (1.4)**	**2 (0.7)**	**1 (0.4)**	**2 (0.8)**	**5 (0.9)**	**4 (0.8)**
Pneumonia	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Sepsis	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Investigations	**3 (1.1)**	**1 (0.4)**	**7 (2.8)**	**8 (3.2)**	**10 (1.9)**	**9 (1.7)**
Platelet count decreased	0	0	6 (2.4)	6 (2.4)	6 (1.1)	6 (1.1)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Neutrophil count decreased	1 (0.4)	0	0	1 (0.4)	1 (0.2)	1 (0.2)
Metabolism and Nutrition Disorders	**4 (1.4)**	**4 (1.4)**	**11 (4.3)**	**7 (2.8)**	**15 (2.8)**	**11 (2.1)**
Decreased appetite	1 (0.4)	1 (0.4)	8 (3.1)	2 (0.8)	9 (1.7)	3 (0.6)
Hypokalaemia	2 (0.7)	1 (0.4)	1 (0.4)	3 (1.2)	3 (0.6)	4 (0.8)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**1 (0.4)**	**2 (0.8)**	**1 (0.2)**	**2 (0.4)**
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**0**	**0**	**1 (0.4)**	**1 (0.4)**	**1 (0.2)**	**1 (0.2)**
Malignant neoplasm progression	0	0	1 (0.4)	0	1 (0.2)	0
Nervous System Disorders	**3 (1.1)**	**2 (0.7)**	**3 (1.2)**	**0**	**6 (1.1)**	**2 (0.4)**
Renal and Urinary Disorders	**1 (0.4)**	**0**	**2 (0.8)**	**0**	**3 (0.6)**	**0**
Acute kidney injury	0	0	2 (0.8)	0	2 (0.4)	0
Respiratory, Thoracic and Mediastinal Disorders	**2 (0.7)**	**1 (0.4)**	**1 (0.4)**	**4 (1.6)**	**3 (0.6)**	**5 (0.9)**
Pulmonary embolism	0	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.2)	3 (0.6)
Respiratory failure	1 (0.4)	0	0	0	1 (0.2)	0
Pleural effusion	0	0	0	2 (0.8)	0	2 (0.4)
Vascular Disorders	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**	**2 (0.4)**	**2 (0.4)**
Hypotension	0	0	1 (0.4)	0	1 (0.2)	0
Deep vein thrombosis	0	1 (0.4)	0	0	0	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.
Source: Table 11 SCS, excerpt and modified

Treatment-emergent adverse events leading to death

Table 128: TEAEs Leading to Death in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Overall	**22 (7.9)**	**24 (8.6)**	**27 (10.6)**	**32 (12.9)**	**49 (9.2)**	**56 (10.6)**
Malignant neoplasm progression	9 (3.2)	12 (4.3)	7 (2.8)	13 (5.2)	16 (3.0)	25 (4.7)
Death	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)	2 (0.4)
Pneumonia	2 (0.7)	1 (0.4)	1 (0.4)	2 (0.8)	3 (0.6)	3 (0.6)
Septic shock	1 (0.4)	0	2 (0.8)	2 (0.8)	3 (0.6)	2 (0.4)
Upper gastrointestinal haemorrhage	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.2)
Cerebral haemorrhage	0	1 (0.4)	2 (0.8)	0	2 (0.4)	1 (0.2)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Disseminated intravascular coagulation	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Respiratory failure	2 (0.7)	0	0	1 (0.4)	2 (0.4)	1 (0.2)
Sepsis	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0
Abdominal infection	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Acute hepatic failure	1 (0.4)	0	0	0	1 (0.2)	0
Acute myocardial infarction	1 (0.4)	1 (0.4)	0	0	1 (0.2)	1 (0.2)
Acute respiratory distress syndrome	0	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Acute respiratory failure	1 (0.4)	0	0	0	1 (0.2)	0
Cardio-respiratory arrest	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.2)	2 (0.4)
COVID-19 pneumonia	1 (0.4)	0	0	0	1 (0.2)	0
Dyspnoea	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Encephalopathy	1 (0.4)	0	0	0	1 (0.2)	0
Gastric perforation	0	0	1 (0.4)	0	1 (0.2)	0
Haemorrhagic ascites	0	0	1 (0.4)	0	1 (0.2)	0
Intestinal obstruction	1 (0.4)	0	0	0	1 (0.2)	0
Klebsiella sepsis	0	0	1 (0.4)	0	1 (0.2)	0
Neutropenic sepsis	1 (0.4)	0	0	1 (0.4)	1 (0.2)	1 (0.2)
Platelet count decreased	0	0	1 (0.4)	0	1 (0.2)	0
Procedural complication	0	0	1 (0.4)	0	1 (0.2)	0
Pulmonary sepsis	1 (0.4)	0	0	0	1 (0.2)	0
Small intestinal obstruction	1 (0.4)	0	0	0	1 (0.2)	0
Sudden death	0	0	1 (0.4)	0	1 (0.2)	0
Syncope	0	0	1 (0.4)	0	1 (0.2)	0
Abscess soft tissue	0	1 (0.4)	0	0	0	1 (0.2)
Acidosis	0	0	0	1 (0.4)	0	1 (0.2)
Cardiac arrest	0	1 (0.4)	0	0	0	1 (0.2)
Diarrhoea	0	0	0	1 (0.4)	0	1 (0.2)
Escherichia infection	0	0	0	1 (0.4)	0	1 (0.2)
Febrile neutropenia	0	0	0	1 (0.4)	0	1 (0.2)
Gastrointestinal haemorrhage	0	1 (0.4)	0	0	0	1 (0.2)
Gastrointestinal obstruction	0	1 (0.4)	0	0	0	1 (0.2)
General physical health deterioration	0	1 (0.4)	0	0	0	1 (0.2)
Haematemesis	0	0	0	1 (0.4)	0	1 (0.2)
Hyperkalaemia	0	0	0	1 (0.4)	0	1 (0.2)
Intestinal perforation	0	1 (0.4)	0	0	0	1 (0.2)
Lower respiratory tract infection viral	0	0	0	1 (0.4)	0	1 (0.2)
Metastases to meninges	0	0	0	1 (0.4)	0	1 (0.2)

MedDRA v25.0 Preferred Term, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Mucosal infection	0	0	0	1 (0.4)	0	1 (0.2)
Pleural effusion	0	0	0	1 (0.4)	0	1 (0.2)
Pulmonary embolism	0	0	0	1 (0.4)	0	1 (0.2)
Renal failure	0	0	0	1 (0.4)	0	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022

Zolbetuximab- or placebo-related TEAEs leading to death

Table 129: Zolbetuximab- or Placebo-related TEAEs which led to Death, by System Organ Class and Preferred Term, in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Overall	**8 (1.5)**	**6 (1.1)**
Blood and lymphatic system disorders	**1 (0.2)**	**0**
Disseminated intravascular coagulation	1 (0.2)	0
Cardiac disorders	**1 (0.2)**	**1 (0.2)**
Acute myocardial infarction	1 (0.2)	0
Cardiac arrest	0	1 (0.2)
Gastrointestinal disorders	**1 (0.2)**	**1 (0.2)**
Upper gastrointestinal haemorrhage	1 (0.2)	0
Haematemesis	0	1 (0.2)
General disorders and administration site conditions	**0**	**3 (0.6)**
Death	0	2 (0.4)
General physical health deterioration	0	1 (0.2)
Infections and infestations	**4 (0.8)**	**1 (0.2)**
Sepsis	2 (0.4)	0
Neutropenic sepsis	1 (0.2)	0
Pneumonia	1 (0.2)	0
Septic shock	0	1 (0.2)
Investigations	**1 (0.2)**	**0**
Platelet count decreased	1 (0.2)	0
Nervous system disorders	**2 (0.4)**	**0**
Cerebral haemorrhage	1 (0.2)	0
Syncope	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.2)**	**0**
Respiratory failure	1 (0.2)	0

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Adverse events of special interest (AESIs)

Based on observations during the clinical development of zolbetuximab, the group terms "Nausea", "Vomiting", "Abdominal Pain", "Hypersensitivity Reactions", "IRRs", "Anemia" and "Neutropenia" were considered AESIs. The search strategy used for the AESIs in the integrated analysis differed from the SPOTLIGHT and GLOW CSRs. For the integrated analysis of AESIs, additional PTs were added to form the group terms as shown below:

- Nausea: PT nausea
- Vomiting: PTs of vomiting, vomiting projectile, retching and cyclic vomiting syndrome
- Abdominal Pain: PTs of abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, abdominal distension, abdominal symptom, abdominal tenderness, gastrointestinal pain and epigastric discomfort
- Hypersensitivity Reactions: hypersensitivity SMQ broad
- IRRs: IRR flagged by investigator and potential IRRs
- Anemia: hematopoietic erythropenia SMQ broad
- Neutropenia: PTs of febrile neutropenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased and neutropenic colitis

Nausea, vomiting and abdominal pain

Table 130: Summary of TEAEs of Interest: Nausea, Vomiting and Abdominal Pain in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

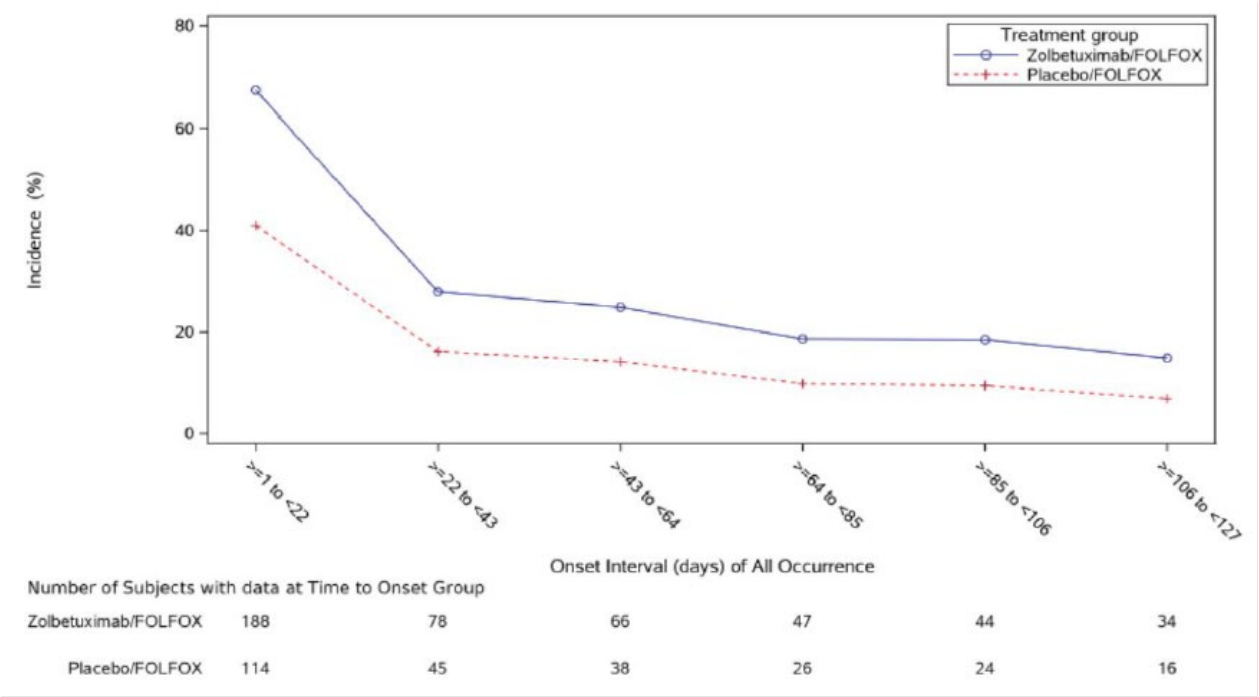
	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
MedDRA (v25.0) TEAE of Interest Category, n (%)	**Zolbetuximab + mFOLFOX6 (n = 279)**	**Placebo + mFOLFOX6 (n = 278)**	**Zolbetuximab + CAPOX (n = 254)**	**Placebo + CAPOX (n = 249)**	**Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)**	**Placebo + mFOLFOX6 or CAPOX (n = 527)**
Nausea Based on PTs	**230 (82.4)**	**169 (60.8)**	**174 (68.5)**	**125 (50.2)**	**404 (75.8)**	**294 (55.8)**
NCI-CTCAE Grade†‡						
Grade 1	74 (26.5)	105 (37.8)	82 (32.3)	75 (30.1)	156 (29.3)	180 (34.2)
Grade 2	111 (39.8)	46 (16.5)	70 (27.6)	44 (17.7)	181 (34.0)	90 (17.1)
Grade 3	45 (16.1)	18 (6.5)	22 (8.7)	6 (2.4)	67 (12.6)	24 (4.6)
Serious	19 (6.8)	11 (4.0)	11 (4.3)	6 (2.4)	30 (5.6)	17 (3.2)
Leading to discontinuation of any study drug	18 (6.5)	3 (1.1)	6 (2.4)	3 (1.2)	24 (4.5)	6 (1.1)
Leading to dose interruption of any study drug	106 (38.0)	9 (3.2)	55 (21.7)	9 (3.6)	161 (30.2)	18 (3.4)
Vomiting Based on PTs	**188 (67.4)**	**101 (36.3)**	**169 (66.5)**	**77 (30.9)**	**357 (67.0)**	**178 (33.8)**
NCI-CTCAE Grade†						
Grade 1	58 (20.8)	59 (21.2)	58 (22.8)	37 (14.9)	116 (21.8)	96 (18.2)
Grade 2	85 (30.5)	26 (9.4)	80 (31.5)	31 (12.4)	165 (31.0)	57 (10.8)
Grade 3	45 (16.1)	16 (5.8)	31 (12.2)	9 (3.6)	76 (14.3)	25 (4.7)
Serious	23 (8.2)	14 (5.0)	15 (5.9)	11 (4.4)	38 (7.1)	25 (4.7)
Leading to discontinuation of any study drug	20 (7.2)	1 (0.4)	9 (3.5)	4 (1.6)	29 (5.4)	5 (0.9)
Leading to dose interruption of any study drug	93 (33.3)	8 (2.9)	71 (28.0)	12 (4.8)	164 (30.8)	20 (3.8)
Abdominal Pain Based on PTs	**112 (40.1)**	**114 (41.0)**	**69 (27.2)**	**78 (31.3)**	**181 (34.0)**	**192 (36.4)**
NCI-CTCAE Grade†‡						
Grade 1	55 (19.7)	67 (24.1)	25 (9.8)	40 (16.1)	80 (15.0)	107 (20.3)
Grade 2	39 (14.0)	41 (14.7)	41 (16.1)	31 (12.4)	80 (15.0)	72 (13.7)
Grade 3	18 (6.5)	6 (2.2)	3 (1.2)	7 (2.8)	21 (3.9)	13 (2.5)
Serious	6 (2.2)	10 (3.6)	4 (1.6)	7 (2.8)	10 (1.9)	17 (3.2)
Leading to discontinuation of any study drug	2 (0.7)	1 (0.4)	4 (1.6)	1 (0.4)	6 (1.1)	2 (0.4)

MedDRA (v25.0) TEAE of Interest Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Leading to dose interruption of any study drug	31 (11.1)	3 (1.1)	17 (6.7)	5 (2.0)	48 (9.0)	8 (1.5)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

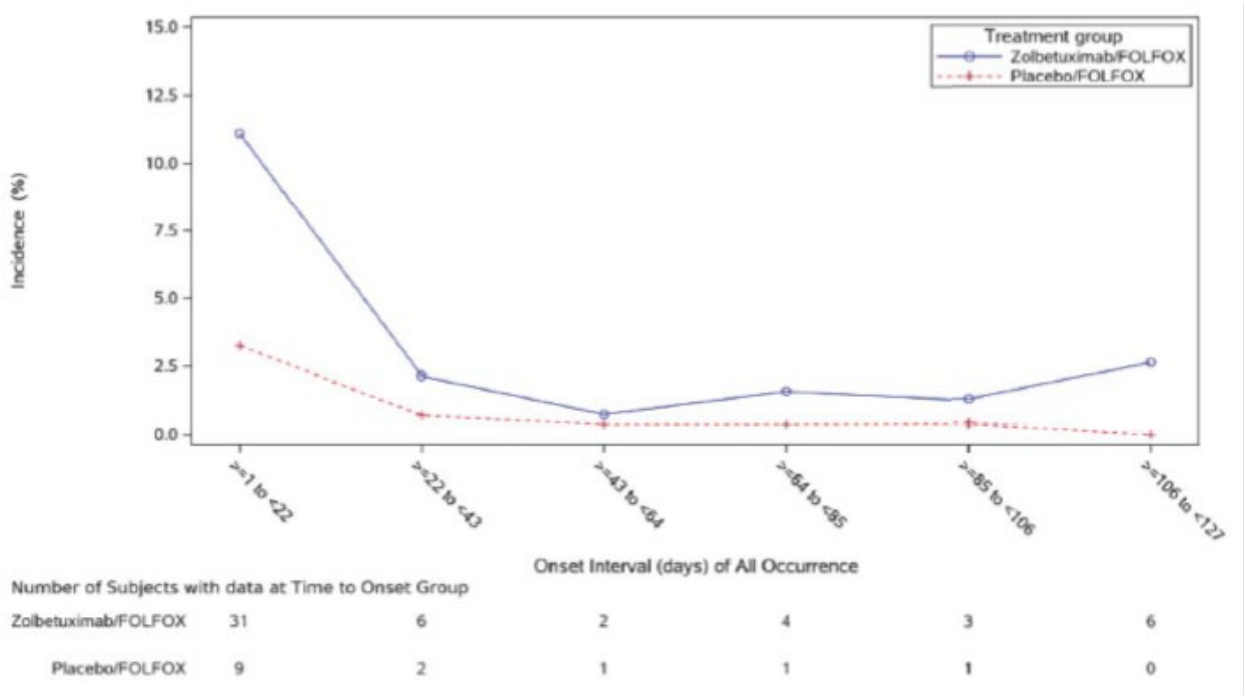
In SPOTLIGHT, in most of the participants with "Nausea" events, the first event occurred within the first 21 days after the start of the first infusion in cycle 1 (in 67.4% of participants in the zolbetuximab plus mFOLFOX6 arm and 40.6% of participants in the placebo plus mFOLFOX6 arm). For all occurrences and all grades of nausea (PT), the highest incidence was observed following the first infusion in both arms [see **Figure 28**].

Figure 25: Summary of All Occurrence of Nausea by Time Interval in the SPOTLIGHT Study (All Grades) (SAF)



In participants with Grade 3 "Nausea" events, the first Grade 3 nausea (PT) occurred within the first 21 days after the start of the first infusion in cycle 1 in 11.1% of participants in the zolbetuximab plus mFOLFOX6 arm and 3.2% of participants in the placebo plus mFOLFOX6 arm. For all occurrences of Grade 3 nausea (PT), the highest incidence was observed following the first infusion in both arms (see **Figure 29**)

Figure 26: Summary of All Occurrence of Nausea by Time Interval (Grade 3) in the SPOTLIGHT Study (SAF)

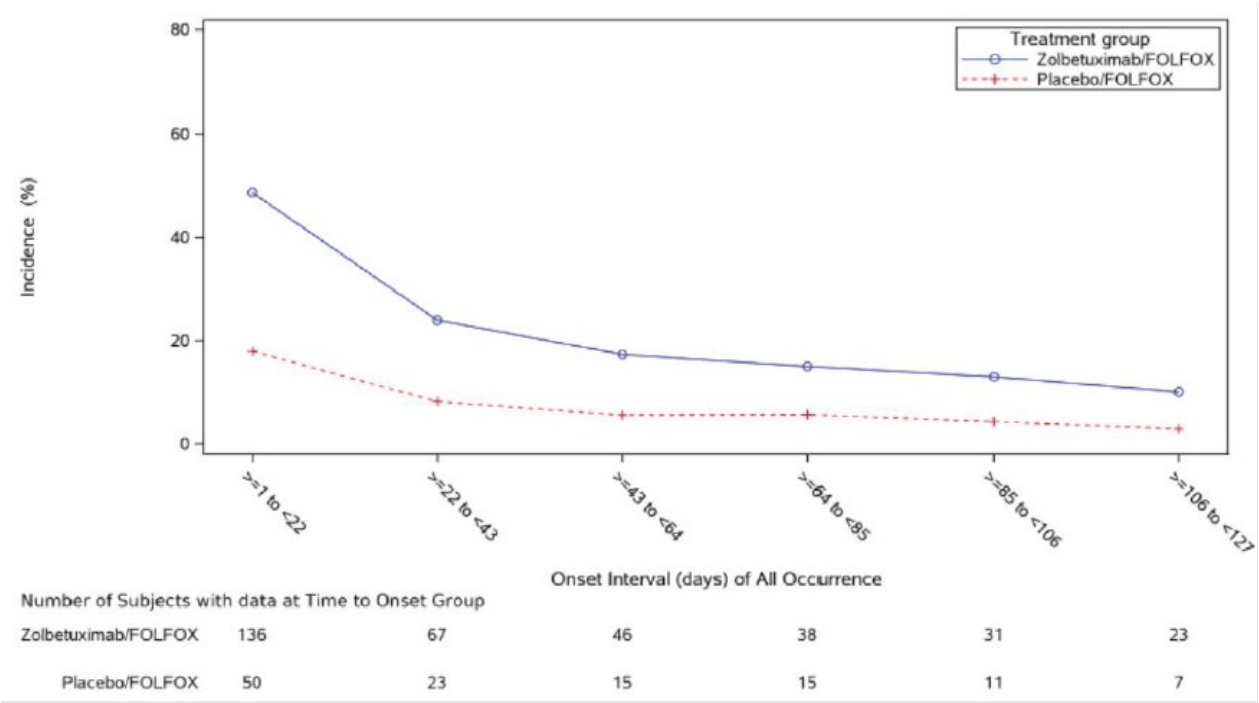


Source: Figure 2 SCS

A similar pattern for the occurrence of nausea was reported in GLOW (data not shown).

In SPOTLIGHT, in most of the participants with "Vomiting" events, the first event occurred within the first 21 days after the start of the first infusion in cycle 1 (in 48.7% of participants in the zolbetuximab plus mFOLFOX6 arm and 17.3% of participants in the placebo plus mFOLFOX6 arm) [ISS Table 9.6.1.16.2.1]. For all occurrences and all grades of vomiting (PT), the highest incidence was observed following the first infusion in both arms [see **Figure 30.**

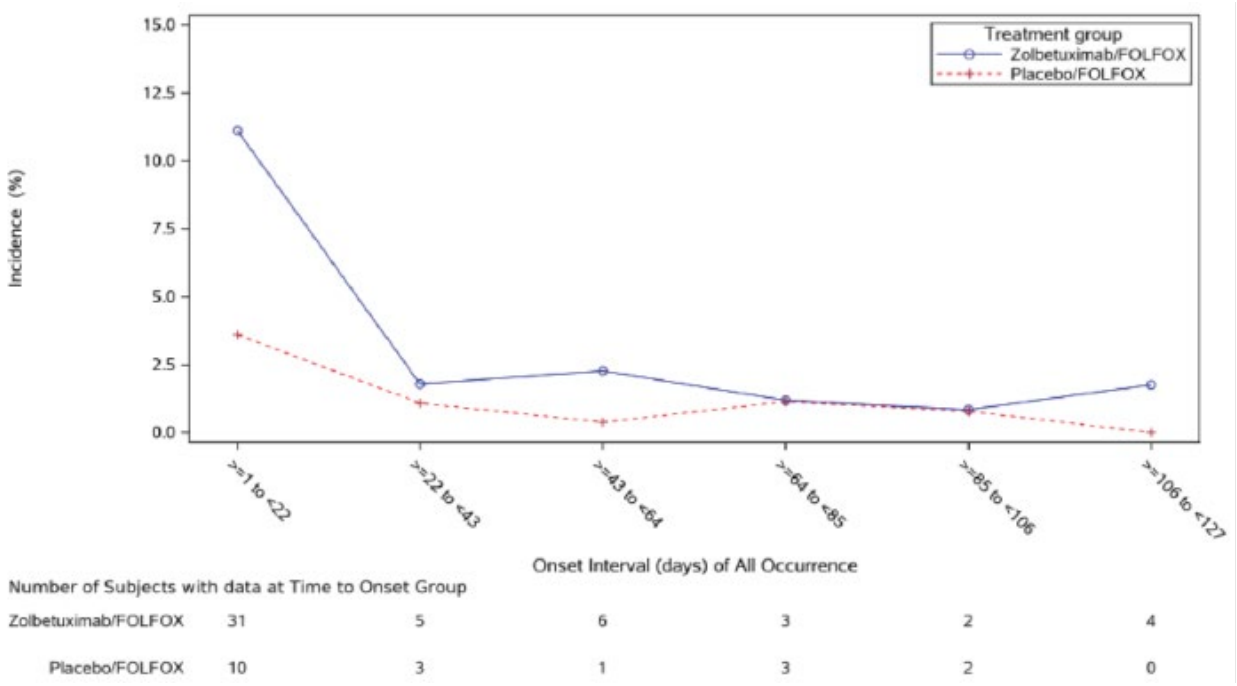
Figure 27: Summary of All Occurrence of Vomiting by Time Interval in the SPOTLIGHT Study (All Grades) (SAF)



In participants with Grade 3 "Vomiting" events, the first Grade 3 vomiting (PT) occurred within the first 21 days after the start of the first infusion in cycle 1 in 11.1% of participants in the zolbetuximab plus mFOLFOX6 arm and 3.6% of participants in the placebo plus mFOLFOX6 arm. For all occurrences of Grade 3 vomiting (PT), the highest incidence was observed following the first infusion in both arms (see

Figure 31).

Figure 28: Summary of All Occurrence of Vomiting by Time Interval in the SPOTLIGHT Study (Grade ≥ 3) (SAF)



A similar pattern for the occurrence of vomiting was reported in GLOW (data not shown).

Hypersensitivity reactions

Table 131: Treatment-emergent Hypersensitivity Reactions (SMQ Broad Preferred Terms), by System Organ Class and Preferred Term, in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any Hypersensitivity Reaction†	**133 (47.7)**	**125 (45.0)**	**58 (22.8)**	**45 (18.1)**	**191 (35.8)**	**170 (32.3)**
NCI-CTCAE Grade‡						
Grade 1	68 (24.4)	70 (25.2)	26 (10.2)	28 (11.2)	94 (17.6)	98 (18.6)
Grade 2	45 (16.1)	49 (17.6)	25 (9.8)	10 (4.0)	70 (13.1)	59 (11.2)
Grade 3	15 (5.4)	6 (2.2)	6 (2.4)	5 (2.0)	21 (3.9)	11 (2.1)
Grade 4	2 (0.7)	0	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.2)
Grade 5	3 (1.1)	0	0	1 (0.4)	3 (0.6)	1 (0.2)
Serious	11 (3.9)	2 (0.7)	8 (3.1)	6 (2.4)	19 (3.6)	8 (1.5)
Leading to discontinuation of any study drug	10 (3.6)	12 (4.3)	7 (2.8)	2 (0.8)	17 (3.2)	14 (2.7)
Leading to dose interruption of any study drug	22 (7.9)	17 (6.1)	15 (5.9)	7 (2.8)	37 (6.9)	24 (4.6)
Leading to dose reduction of any study drug	8 (2.9)	2 (0.7)	4 (1.6)	0	12 (2.3)	2 (0.4)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Leading to dose rate reduction of any study drug	3 (1.1)	1 (0.4)	1 (0.4)	0	4 (0.8)	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

The PTs drug hypersensitivity and anaphylactic reaction were listed among the SOC "immune system disorders" and contributed to the overall frequencies of the pooled term "hypersensitivity reaction" with incidences of 1.1% in the combined phase 3 zolbetuximab group and 1.7% in the combined phase 3 control group (drug hypersensitivity) and 0.6% in the combined phase 3 zolbetuximab group and 0.9% in the combined phase 3 control group (anaphylactic reactions), see Table 3-3-7-18.

Table 132: Treatment-emergent Hypersensitivity Reactions (SMQ Broad Preferred Terms), by System Organ Class and Preferred Term, in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any Hypersensitivity Reaction†	**191 (35.8)**	**170 (32.3)**
Blood and Lymphatic System Disorders	**2 (0.4)**	**0**
Eosinophilia	2 (0.4)	0
Eye Disorders	**4 (0.8)**	**0**
Eyelid oedema	2 (0.4)	0
Periorbital oedema	2 (0.4)	0
Gastrointestinal Disorders	**80 (15.0)**	**72 (13.7)**
Stomatitis	66 (12.4)	64 (12.1)
Mouth ulceration	10 (1.9)	5 (0.9)
Cheilitis	5 (0.9)	2 (0.4)
Lip swelling	3 (0.6)	1 (0.2)
Gastrointestinal oedema	1 (0.2)	0
Swollen tongue	1 (0.2)	0
Mouth swelling	0	1 (0.2)
Oedema mouth	0	1 (0.2)
General Disorders and Administration Site Conditions	**11 (2.1)**	**6 (1.1)**
Face oedema	5 (0.9)	4 (0.8)
Generalised oedema	4 (0.8)	0
Swelling face	2 (0.4)	0
Catheter site rash	0	1 (0.2)
Localised oedema	0	1 (0.2)
Immune System Disorders	**14 (2.6)**	**18 (3.4)**
Drug hypersensitivity	6 (1.1)	9 (1.7)
Anaphylactic reaction	3 (0.6)	5 (0.9)
Hypersensitivity	2 (0.4)	2 (0.4)
Seasonal allergy	2 (0.4)	1 (0.2)
Contrast media allergy	1 (0.2)	0
Contrast media reaction	0	1 (0.2)
Infections and Infestations	**10 (1.9)**	**5 (0.9)**

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Conjunctivitis	8 (1.5)	4 (0.8)
Rash pustular	2 (0.4)	1 (0.2)
Injury, Poisoning and Procedural Complications	**17 (3.2)**	**7 (1.3)**
Infusion-related reaction	17 (3.2)	7 (1.3)
Reproductive System and Breast Disorders	**0**	**1 (0.2)**
Scrotal swelling	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**16 (3.0)**	**13 (2.5)**
Acute respiratory failure	4 (0.8)	0
Respiratory failure	4 (0.8)	2 (0.4)
Interstitial lung disease	3 (0.6)	1 (0.2)
Pneumonitis	2 (0.4)	3 (0.6)
Bronchospasm	1 (0.2)	0
Choking	1 (0.2)	0
Laryngospasm	1 (0.2)	3 (0.6)
Throat tightness	1 (0.2)	1 (0.2)
Wheezing	1 (0.2)	0
Asthma	0	1 (0.2)
Rhinitis allergic	0	2 (0.4)
Skin and Subcutaneous Tissue Disorders	**96 (18.0)**	**97 (18.4)**
Pruritus	33 (6.2)	32 (6.1)
Rash	23 (4.3)	28 (5.3)
Rash maculo-papular	13 (2.4)	22 (4.2)
Erythema	10 (1.9)	13 (2.5)
Dermatitis acneiform	8 (1.5)	2 (0.4)
Urticaria	8 (1.5)	9 (1.7)
Dermatitis	4 (0.8)	3 (0.6)
Skin exfoliation	4 (0.8)	0
Eczema	3 (0.6)	2 (0.4)
Rash erythematous	3 (0.6)	2 (0.4)
Skin erosion	3 (0.6)	0
Dermatitis contact	2 (0.4)	1 (0.2)
Drug eruption	2 (0.4)	0
Rash macular	2 (0.4)	3 (0.6)
Blister	1 (0.2)	2 (0.4)
Cutaneous vasculitis	1 (0.2)	0
Dermatitis allergic	1 (0.2)	0
Dermatitis atopic	1 (0.2)	0
Dermatitis bullous	1 (0.2)	2 (0.4)
Rash pruritic	1 (0.2)	2 (0.4)
Skin necrosis	1 (0.2)	0
Dermatitis exfoliative generalized	0	1 (0.2)
Eczema nummular	0	1 (0.2)
Erythema multiforme	0	1 (0.2)
Exfoliative rash	0	3 (0.6)
Photosensitivity reaction	0	1 (0.2)
Vascular Disorders	**11 (2.1)**	**5 (0.9)**
Flushing	11 (2.1)	5 (0.9)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Infusion-related reactions (by Investigator)

IRRs were defined as events occurring during the infusion or within 1 day of the infusion.

Table 133: Summary of TEAEs of Interest: Infusion-related Reactions (Assessed by Investigator) in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
Category, n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any IRR (Assessed by Investigator)	**124 (44.4)**	**33 (11.9)**	**91 (35.8)**	**25 (10.0)**	**215 (40.3)**	**58 (11.0)**
NCI-CTCAE Grade†						
Grade 1	22 (7.9)	10 (3.6)	21 (8.3)	9 (3.6)	43 (8.1)	19 (3.6)
Grade 2	82 (29.4)	21 (7.6)	53 (20.9)	15 (6.0)	135 (25.3)	36 (6.8)
Grade 3	20 (7.2)	1 (0.4)	16 (6.3)	1 (0.4)	36 (6.8)	2 (0.4)
Grade 4	0	1 (0.4)	1 (0.4)	0	1 (0.2)	1 (0.2)
Serious	8 (2.9)	0	9 (3.5)	0	17 (3.2)	0
Leading to discontinuation of any study drug	17 (6.1)	11 (4.0)	10 (3.9)	1 (0.4)	27 (5.1)	12 (2.3)
Leading to dose interruption of any study drug	89 (31.9)	15 (5.4)	60 (23.6)	12 (4.8)	149 (28.0)	27 (5.1)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Investigator-assessed IRRs included PTs of the most common symptoms observed with IRR (nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough and hypertension). TEAEs flagged by the investigator as "infusion-related reaction" were additionally assessed as individual TEAEs occurring during the trial.

The PT infusion-related reaction was listed among the SOC "injury, poisoning and procedural complications" and contributed to the overall frequency of the pooled term "IRRs by Investigator" with incidences of 3.2% in the combined phase 3 zolbetuximab group and 1.3% in the combined phase 3 control group, see Table 3-3-7-20.

Table 134: Excerpt of Treatment-emergent Infusion-related Reactions (Assessed by Investigator), by System Organ Class and Preferred Term, in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any IRR (Assessed by Investigator)	**215 (40.3)**	**58 (11.0)**
Blood and Lymphatic System Disorders	**5 (0.9)**	**5 (0.9)**
Anaemia	3 (0.6)	1 (0.2)
Thrombocytopenia	3 (0.6)	3 (0.6)
Neutropenia	2 (0.4)	3 (0.6)
Cardiac Disorders	**3 (0.6)**	**0**
Tachycardia	3 (0.6)	0
Gastrointestinal Disorders	**174 (32.6)**	**22 (4.2)**
Nausea	128 (24.0)	15 (2.8)
Vomiting	114 (21.4)	8 (1.5)
Abdominal pain	20 (3.8)	4 (0.8)
Abdominal pain upper	10 (1.9)	0
Salivary hypersecretion	7 (1.3)	0
Diarrhoea	5 (0.9)	3 (0.6)
Dyspepsia	4 (0.8)	0
General Disorders and Administration Site Conditions	**44 (8.3)**	**13 (2.5)**
Chills	13 (2.4)	2 (0.4)
Pyrexia	9 (1.7)	2 (0.4)
Chest discomfort	8 (1.5)	2 (0.4)
Non-cardiac chest pain	6 (1.1)	1 (0.2)
Malaise	4 (0.8)	0
Chest pain	3 (0.6)	0
Immune System Disorders	**8 (1.5)**	**7 (1.3)**
Drug hypersensitivity	4 (0.8)	4 (0.8)
Anaphylactic reaction	3 (0.6)	3 (0.6)
Injury, Poisoning and Procedural Complications	**21 (3.9)**	**8 (1.5)**
Infusion-related reaction	17 (3.2)	7 (1.3)
Musculoskeletal and Connective Tissue Disorders	**7 (1.3)**	**1 (0.2)**
Back pain	6 (1.1)	0
Nervous System Disorders	**17 (3.2)**	**8 (1.5)**
Headache	5 (0.9)	0
Dizziness	4 (0.8)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	**17 (3.2)**	**6 (1.1)**
Cough	6 (1.1)	0
Dyspnoea	6 (1.1)	4 (0.8)
Skin and Subcutaneous Tissue Disorders	**15 (2.8)**	**18 (3.4)**
Erythema	5 (0.9)	4 (0.8)
Pruritus	5 (0.9)	6 (1.1)
Hyperhidrosis	4 (0.8)	4 (0.8)
Rash	1 (0.2)	3 (0.6)
Vascular Disorders	**25 (4.7)**	**8 (1.5)**
Hypertension	13 (2.4)	1 (0.2)
Flushing	8 (1.5)	4 (0.8)
Hot flush	5 (0.9)	1 (0.2)
Hypotension	4 (0.8)	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Anaemia

Table 135: Summary of TEAEs of Interest: Anaemia in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any Event of Anemia†	**102 (36.6)**	**104 (37.4)**	**90 (35.4)**	**92 (36.9)**	**192 (36.0)**	**196 (37.2)**
NCI-CTCAE Grade‡						
Grade 1	36 (12.9)	32 (11.5)	30 (11.8)	27 (10.8)	66 (12.4)	59 (11.2)
Grade 2	41 (14.7)	46 (16.5)	33 (13.0)	37 (14.9)	74 (13.9)	83 (15.7)
Grade 3	24 (8.6)	24 (8.6)	25 (9.8)	26 (10.4)	49 (9.2)	50 (9.5)
Grade 4	1 (0.4)	2 (0.7)	2 (0.8)	2 (0.8)	3 (0.6)	4 (0.8)
Grade 5	0	0	0	0	0	0
Serious	5 (1.8)	4 (1.4)	5 (2.0)	6 (2.4)	10 (1.9)	10 (1.9)
Leading to discontinuation of any study drug	4 (1.4)	3 (1.1)	0	3 (1.2)	4 (0.8)	6 (1.1)
Leading to dose interruption of any study drug	10 (3.6)	8 (2.9)	6 (2.4)	10 (4.0)	16 (3.0)	18 (3.4)
Leading to dose reduction of any study drug	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.4)	3 (0.6)	3 (0.6)
Leading to dose rate reduction of any study drug	0	0	0	0	0	0

Neutropenia

Table 136: Summary of TEAEs of Interest: Neutropenia in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Any Event of Neutropenia	**187 (67.0)**	**179 (64.4)**	**118 (46.5)**	**95 (38.2)**	**305 (57.2)**	**274 (52.0)**
NCI-CTCAE Grade†						
Grade 1	5 (1.8)	6 (2.2)	11 (4.3)	11 (4.4)	16 (3.0)	17 (3.2)
Grade 2	35 (12.5)	42 (15.1)	63 (24.8)	49 (19.7)	98 (18.4)	91 (17.3)
Grade 3	109 (39.1)	96 (34.5)	38 (15.0)	29 (11.6)	147 (27.6)	125 (23.7)
Grade 4	37 (13.3)	35 (12.6)	6 (2.4)	4 (1.6)	43 (8.1)	39 (7.4)
Grade 5	1 (0.4)	0	0	2 (0.8)	1 (0.2)	2 (0.4)
Serious	16 (5.7)	8 (2.9)	5 (2.0)	7 (2.8)	21 (3.9)	15 (2.8)
Leading to discontinuation of any study drug	33 (11.8)	28 (10.1)	7 (2.8)	7 (2.8)	40 (7.5)	35 (6.6)
Leading to dose interruption of any study drug	79 (28.3)	79 (28.4)	49 (19.3)	30 (12.0)	128 (24.0)	109 (20.7)
Leading to dose reduction of any study drug	83 (29.7)	69 (24.8)	37 (14.6)	27 (10.8)	120 (22.5)	96 (18.2)

Category, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Leading to dose rate reduction of any study drug	2 (0.7)	0	1 (0.4)	1 (0.4)	3 (0.6)	1 (0.2)

Adverse drug reactions (ADRs)

TEAEs that have been determined to be associated with zolbetuximab are considered to be ADRs. The basis for the identification of ADRs was the **integrated analysis of phase 2 (FAST, ILUSTRO) and phase 3 (SPOTLIGHT, GLOW) studies**, in which zolbetuximab was administered at the claimed dose of 800/600 mg/m² Q3W in combination with chemotherapy.

ADRs were evaluated using the following quantitative criteria:

- Incidence of TEAEs of at least 2% in the combined phase 2 and 3 zolbetuximab group.
- Incidence greater than at least 2% compared with the combined phase 2 and 3 control group.

The list of potential ADRs meeting the criteria included neutropenia, nausea, vomiting, abdominal pain upper, dyspepsia, salivary hypersecretion, oedema peripheral, malaise, chills, neutrophil count decreased, weight decreased, white blood cell count decreased, decreased appetite, hypoalbuminaemia, hypocalcaemia, insomnia, and hypertension.

A medical review for each of these potential events above and the events that did not meet the potential ADR threshold was conducted to further assess the plausibility of an association between zolbetuximab treatment and the event. Medical review focused upon the following criteria:

- biologic plausibility,
- relative time to onset of the event after exposure to zolbetuximab,
- confounding factors such as demographics, concomitant medications, past medical history,
- common comorbidities or background rates of risks in the target patient population,
- supplementary evidence such as laboratory assessments.

The table summarizing frequencies of ADRs as basis for the presentation of ADRs and respective frequency categories in section 4.8 of the SmPC is shown below.

Table 137: Adverse Drug Reactions by Frequency Categories (Safety Analysis Set)

System Organ Class	Preferred Term	Integrated FAST/ILUSTRO/SPOTLIGHT/GLOW Studies			
		Zolbetuximab + EOX/mFOLFOX6/CAPOX (n = 631)†		EOX or PBO + mFOLFOX6/CAPOX (n = 611)‡	
		Any grade		Any grade	
		n (%)	Frequency	n (%)	Frequency
Blood and lymphatic system disorders	Neutropenia	194 (30.7)	Very common	158 (25.9)	Very common
	Neutrophil count decreased	179 (28.4)	Very common	152 (24.9)	Very common
Immune system disorders	Drug hypersensitivity	10 (1.6)	Common	10 (1.6)	Common
	Anaphylactic reaction	3 (0.5)	Uncommon	5 (0.8)	Uncommon
Metabolism and nutrition disorders	Hypoalbuminaemia	108 (17.1)	Very common	57 (9.3)	Common
	Decreased appetite	265 (42.0)	Very common	201 (32.9)	Very common

Vascular disorders	Hypertension	57 (9.0)	Common	35 (5.7)	Common
Gastrointestinal disorders	Vomiting	422 (66.9)	Very common	225 (36.8)	Very common
	Nausea	487 (77.2)	Very common	360 (58.9)	Very common
	Dyspepsia	49 (7.8)	Common	32 (5.2)	Common
	Salivary hypersecretion	24 (3.8)	Common	6 (1.0)	Common
General disorders and administration site conditions	Pyrexia	110 (17.4)	Very common	90 (14.7)	Very common
	Oedema peripheral	88 (13.9)	Very common	38 (6.2)	Common
	Chills	33 (5.2)	Common	17 (2.8)	Common
Investigations	Weight decreased	138 (21.9)	Very common	105 (17.2)	Very common
Injury, poisoning and procedural complications	Infusion related reaction	20 (3.2)	Common	7 (1.1)	Common

Data cut-off date 08 Sep 2023 for SPOTLIGHT and 12 January 2024 for GLOW

Based on the final **integrated phase 2 and phase 3 safety analysis** (data cut-off date 08 September 2023 for SPOTLIGHT and 12 January 2024 for GLOW), serious adverse reactions occurred in 16% of patients treated with zolbetuximab. The most common serious adverse reactions were vomiting (4.3%), nausea (3.6%), and decreased appetite (1.6%).

Twenty percent of patients permanently discontinued zolbetuximab for adverse reactions; the most common adverse reactions leading to dose discontinuation were vomiting (3.8%) and nausea (3.3%).

Adverse reactions leading to dose interruption of zolbetuximab occurred in 49.6% of patients; the most common adverse reactions leading to dose interruption were vomiting (26.1%), nausea (24.6%), neutropenia (4.8%), hypertension (3%), neutrophil count decreased (2.5%), chills (2.1%), infusion related reaction (1.6%), decreased appetite (1.3%) and dyspepsia (1.1%).

Nausea and vomiting

All grade nausea and vomiting occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 77.2% and 66.9%, respectively. Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment. The median time to onset of nausea and vomiting was 1 day each with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy. The median duration of nausea and vomiting was 3 days and 1 day, respectively, with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy.

Severe (Grade 3) nausea and vomiting occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 11.6% and 13.6%. . The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 9.7% of patients due to nausea and in 7.8% of patients due to vomiting.

Hypersensitivity reactions

All grade anaphylactic reaction and drug hypersensitivity occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 0.5% and 1.6%, respectively.

Severe (Grade 3) anaphylactic reaction and drug hypersensitivity occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 0.5% and 0.2%.

Anaphylactic reaction led to permanent discontinuation of zolbetuximab in 0.3% of patients. Dose interruption of zolbetuximab was experienced due to drug hypersensitivity in 0.3% of patients.

The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 0.2% of patients due to drug hypersensitivity.

The median time to onset of anaphylactic reaction and drug hypersensitivity was 22 days and 113 days, respectively, with zolbetuximab in combination with chemotherapy.

Infusion-related reactions

All grade IRR occurred with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy at a frequency of 3.2%.

Severe (Grade 3) IRR occurred in 0.5% of patients treated with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy.

An IRR led to permanent discontinuation of zolbetuximab in 0.5% of patients, and dose interruption in 1.6% of patients. The infusion rate was reduced for zolbetuximab or fluoropyrimidine and platinum-containing chemotherapy in 0.2% of patients due to an IRR.

2.6.8.4. Laboratory findings

Haematology

NCI-CTCAE Grade 3 or Grade 4 clinical haematology laboratory results, based on values from the central laboratory, are summarized in **Table 140**.

Table 138: NCI-CTCAE Grade 3 or 4 Clinical Haematology Results (Central Laboratory), in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
Laboratory Parameter (Grade/Direction), n (%)	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Hemoglobin (Grade 3/low)	17 (6.1)	24 (8.6)	9 (3.5)	10 (4.0)	26 (4.9)	34 (6.5)
Hemoglobin (Grade 4/low)	0	0	0	0	0	0
Leukocytes (Grade 3/low)	14 (5.0)	34 (12.2)	3 (1.2)	8 (3.2)	17 (3.2)	42 (8.0)
Leukocytes (Grade 4/low)	1 (0.4)	3 (1.1)	0	0	1 (0.2)	3 (0.6)
Lymphocytes (Grade 3/low)	34 (12.2)	26 (9.4)	17 (6.7)	14 (5.6)	51 (9.6)	40 (7.6)
Lymphocytes (Grade 4/low)	1 (0.4)	2 (0.7)	2 (0.8)	0	3 (0.6)	2 (0.4)
Neutrophils (Grade 3/low)	49 (17.6)	66 (23.7)	14 (5.5)	13 (5.2)	63 (11.8)	79 (15.0)
Neutrophils (Grade 4/low)	14 (5.0)	8 (2.9)	1 (0.4)	0	15 (2.8)	8 (1.5)
Platelets (Grade 3/low)	2 (0.7)	7 (2.5)	1 (0.4)	5 (2.0)	3 (0.6)	12 (2.3)
Platelets (Grade 4/low)	0	0	1 (0.4)	0	1 (0.2)	0

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Chemistry

NCI-CTCAE Grade 3 or Grade 4 clinical chemistry laboratory results, based on values from the central laboratory, are summarized in **Table 141**.

Table 139: NCI-CTCAE Grade 3 or 4 Clinical Chemistry Results (Central Laboratory), in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Laboratory Parameter (Grade/Direction), n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (n = 279)	Placebo + mFOLFOX6 (n = 278)	Zolbetuximab + CAPOX (n = 254)	Placebo + CAPOX (n = 249)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Alanine aminotransferase (G3/high)	2 (0.7)	3 (1.1)	1 (0.4)	4 (1.6)	3 (0.6)	7 (1.3)
Alanine aminotransferase (G4/high)	0	0	0	1 (0.4)	0	1 (0.2)
Alkaline phosphatase (G3/high)	5 (1.8)	9 (3.2)	6 (2.4)	7 (2.8)	11 (2.1)	16 (3.0)
Alkaline phosphatase (G4/high)	1 (0.4)	0	0	0	1 (0.2)	0
Aspartate aminotransferase (G3/high)	5 (1.8)	4 (1.4)	2 (0.8)	5 (2.0)	7 (1.3)	9 (1.7)
Aspartate aminotransferase (G4/high)	0	0	0	1 (0.4)	0	1 (0.2)
Bilirubin (Grade 3/high)	1 (0.4)	2 (0.7)	3 (1.2)	1 (0.4)	4 (0.8)	3 (0.6)
Bilirubin (Grade 4/high)	0	0	1 (0.4)	2 (0.8)	1 (0.2)	2 (0.4)
Calcium corrected (Grade 4/high)	0	1 (0.4)	0	0	0	1 (0.2)
Creatinine (Grade 3/high)	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (0.6)	1 (0.2)
Glucose (Grade 3/high)	23 (8.2)	21 (7.6)	12 (4.7)	8 (3.2)	35 (6.6)	29 (5.5)
Glucose (Grade 4/high)	5 (1.8)	5 (1.8)	0	0	5 (0.9)	5 (0.9)
Magnesium (Grade 3/high)	0	1 (0.4)	0	0	0	1 (0.2)
Potassium (Grade 3/high)	6 (2.2)	2 (0.7)	3 (1.2)	0	9 (1.7)	2 (0.4)
Sodium (Grade 3/high)	0	0	0	1 (0.4)	0	1 (0.2)
Sodium (Grade 4/high)	0	1 (0.4)	0	0	0	1 (0.2)
Albumin (Grade 3/low)	4 (1.4)	3 (1.1)	3 (1.2)	1 (0.4)	7 (1.3)	4 (0.8)
Calcium corrected (Grade 3/low)	4 (1.4)	5 (1.8)	0	4 (1.6)	4 (0.8)	9 (1.7)
Calcium corrected (Grade 4/low)	2 (0.7)	0	0	1 (0.4)	2 (0.4)	1 (0.2)
Magnesium (Grade 4/low)	0	0	0	1 (0.4)	0	1 (0.2)
Phosphate (Grade 3/low)	28 (10.0)	17 (6.1)	6 (2.4)	9 (3.6)	34 (6.4)	26 (4.9)
Phosphate (Grade 4/low)	2 (0.7)	1 (0.4)	0	0	2 (0.4)	1 (0.2)
Potassium (Grade 3/low)	20 (7.2)	9 (3.2)	4 (1.6)	10 (4.0)	24 (4.5)	19 (3.6)
Potassium (Grade 4/low)	1 (0.4)	4 (1.4)	2 (0.8)	2 (0.8)	3 (0.6)	6 (1.1)
Sodium (Grade 3/low)	10 (3.6)	4 (1.4)	6 (2.4)	7 (2.8)	16 (3.0)	11 (2.1)
Sodium (Grade 4/low)	0	0	0	1 (0.4)	0	1 (0.2)

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

2.6.8.5. Cardiac electrophysiology

In the pivotal phase 3 studies SPOTLIGHT and GLOW, absolute QTcF intervals and changes from baseline in QTcF were summarized for values of clinical importance (> 450 msec).

Table 140: Lead ECG Results: QTcF Intervals in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Parameter Criteria, n (%)	Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Placebo + mFOLFOX6 or CAPOX (n = 527)
Absolute Value at Any Post-baseline Time Point†		
N	499	501
≤ 450 msec	339 (67.9)	338 (67.5)
> 450 msec	160 (32.1)	163 (32.5)
> 450 to ≤ 480 msec	94 (18.8)	96 (19.2)
> 480 msec	66 (13.2)	67 (13.4)

Parameter Criteria, n (%)	Integrated SPOTLIGHT/GLOW Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)	Integrated SPOTLIGHT/GLOW Placebo + mFOLFOX6 or CAPOX (n = 527)
> 480 to ≤ 500 msec	29 (5.8)	23 (4.6)
> 500 msec	37 (7.4)	44 (8.8)
Change From Baseline at Any Post-baseline Time Point†		
N	484	491
≤ 0 msec	40 (8.3)	28 (5.7)
> 0 msec	444 (91.7)	463 (94.3)
> 0 to ≤ 30 msec	213 (44.0)	248 (50.5)
> 30 msec	231 (47.7)	215 (43.8)
> 30 to ≤ 60 msec	157 (32.4)	150 (30.5)
> 60 msec	74 (15.3)	65 (13.2)

2.6.8.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.7. Safety in special populations

Age

Table 141: Common MedDRA Terms in Older Participants by Age in the Integrated Analysis of FAST, ILUSTRO, SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Common MedDRA Term, n (%)	Zolbetuximab + EOX/mFOLFOX6/CAPOX†				EOX or Placebo + mFOLFOX6/CAPOX‡			
	Age < 65 y (n = 405)	Age 65-74 y (n = 188)	Age 75-84 y (n = 38)	Age ≥ 85 y (n = 0)	Age < 65 y (n = 412)	Age 65-74 y (n = 159)	Age 75-84 y (n = 38)	Age ≥ 85 y (n = 2)
TEAEs	402 (99.3)	185 (98.4)	37 (97.4)	0	407 (98.8)	158 (99.4)	38 (100.0)	2 (100.0)
Serious TEAEs	161 (39.8)	96 (51.1)	15 (39.5)	0	180 (43.7)	76 (47.8)	15 (39.5)	1 (50.0)
Fatal	29 (7.2)	21 (11.2)	4 (10.5)	0	46 (11.2)	20 (12.6)	4 (10.5)	1 (50.0)
Hospitalization /prolong existing hospitalization	131 (32.3)	74 (39.4)	12 (31.6)	0	139 (33.7)	58 (36.5)	15 (39.5)	1 (50.0)
Life-threatening	15 (3.7)	9 (4.8)	0	0	10 (2.4)	10 (6.3)	1 (2.6)	0
Disability/incapacity	4 (1.0)	5 (2.7)	0	0	4 (1.0)	1 (0.6)	1 (2.6)	0
Other (Medically significant)	12 (3.0)	10 (5.3)	0	0	11 (2.7)	5 (3.1)	1 (2.6)	0
TEAE leading to drop out	137 (33.8)	78 (41.5)	11 (28.9)	0	108 (26.2)	60 (37.7)	18 (47.4)	1 (50.0)
Psychiatric disorders	56 (13.8)	27 (14.4)	2 (5.3)	0	50 (12.1)	19 (11.9)	5 (13.2)	1 (50.0)
Nervous system disorders	245 (60.5)	131 (69.7)	22 (57.9)	0	260 (63.1)	107 (67.3)	24 (63.2)	2 (100.0)
Accidents and injuries	0	0	0	0	0	0	0	0
Cardiac disorders	38 (9.4)	17 (9.0)	3 (7.9)	0	40 (9.7)	16 (10.1)	3 (7.9)	1 (50.0)
Vascular disorders	90 (22.2)	43 (22.9)	13 (34.2)	0	71 (17.2)	25 (15.7)	8 (21.1)	2 (100.0)
Cerebrovascular disorders	3 (0.7)	1 (0.5)	0	0	0	1 (0.6)	0	0
Infections and infestations	123 (30.4)	61 (32.4)	14 (36.8)	0	115 (27.9)	44 (27.7)	12 (31.6)	1 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures§	47 (11.6)	37 (19.7)	7 (18.4)	0	45 (10.9)	20 (12.6)	4 (10.5)	1 (50.0)

Sex

Table 142: Overview of Safety by Sex in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Male		Female	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 334)	Placebo + mFOLFOX6 or CAPOX (n = 325)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 199)	Placebo + mFOLFOX6 or CAPOX (n = 202)
Any TEAE	**331 (99.1)**	**321 (98.8)**	**198 (99.5)**	**200 (99.0)**
Drug-related TEAE†	328 (98.2)	312 (96.0)	195 (98.0)	190 (94.1)
Zolbetuximab or placebo-related TEAEs†	307 (91.9)	233 (71.7)	179 (89.9)	151 (74.8)
Serious TEAE‡	**158 (47.3)**	**153 (47.1)**	**87 (43.7)**	**92 (45.5)**
Drug-related Serious TEAE†‡	85 (25.4)	56 (17.2)	49 (24.6)	41 (20.3)
Zolbetuximab/ or placebo-related serious TEAEs†‡	61 (18.3)	42 (12.9)	36 (18.1)	25 (12.4)
TEAE Leading to Death	**34 (10.2)**	**37 (11.4)**	**15 (7.5)**	**19 (9.4)**

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Male		Female	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 334)	Placebo + mFOLFOX6 or CAPOX (n = 325)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 199)	Placebo + mFOLFOX6 or CAPOX (n = 202)
TEAE Leading to Permanent Discontinuation of Any Study Drug§	**128 (38.3)**	**102 (31.4)**	**71 (35.7)**	**67 (33.2)**
Drug-related TEAE Leading to Permanent Discontinuation of Any Study Drug†§	101 (30.2)	71 (21.8)	60 (30.2)	50 (24.8)
Drug-related TEAE leading to withdrawal of zolbetuximab or placebo†	32 (9.6)	11 (3.4)	24 (12.1)	6 (3.0)
TEAE Leading to Dose Interruption of Any Study Drug§	**250 (74.9)**	**169 (52.0)**	**159 (79.9)**	**115 (56.9)**
Drug-related TEAE Leading to Dose Interruption of Any Study Drug†§	232 (69.5)	140 (43.1)	150 (75.4)	96 (47.5)
Drug-related TEAE leading to dose interruption of zolbetuximab or placebo†	168 (50.3)	59 (18.2)	116 (58.3)	36 (17.8)
Worst NCI-CTCAE ≥ Grade 3 TEAE¶	**260 (77.8)**	**241 (74.2)**	**167 (83.9)**	**149 (73.8)**
Grade 3	195 (58.4)	171 (52.6)	125 (62.8)	108 (53.5)
Grade 4	31 (9.3)	33 (10.2)	27 (13.6)	22 (10.9)
Grade 5	34 (10.2)	37 (11.4)	15 (7.5)	19 (9.4)
Drug-related Worst NCI-CTCAE Grade TEAE ≥ Grade 3 †¶	213 (63.8)	170 (52.3)	150 (75.4)	117 (57.9)
Grade 3	181 (54.2)	140 (43.1)	122 (61.3)	92 (45.5)
Grade 4	25 (7.5)	23 (7.1)	24 (12.1)	21 (10.4)
Grade 5	7 (2.1)	7 (2.2)	4 (2.0)	4 (2.0)
Zolbetuximab or Placebo-related Worst NCI-CTCAE Grade TEAE ≥ Grade 3 †¶	146 (43.7)	91 (28.0)	101 (50.8)	63 (31.2)
Grade 3	131 (39.2)	73 (22.5)	85 (42.7)	51 (25.2)
Grade 4	10 (3.0)	14 (4.3)	13 (6.5)	10 (5.0)
Grade 5	5 (1.5)	4 (1.2)	3 (1.5)	2 (1.0)

Table 143: TEAEs ≥ Grade 3 Occurring in ≥ 5% of Participants in Any Treatment Group, by Preferred Term, by Sex in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Male		Female	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 334)	Placebo + mFOLFOX6 or CAPOX (n = 325)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 199)	Placebo + mFOLFOX6 or CAPOX (n = 202)
Any TEAE	**260 (77.8)**	**241 (74.2)**	**167 (83.9)**	**149 (73.8)**
Anaemia	24 (7.2)	34 (10.5)	27 (13.6)	20 (9.9)
Asthenia	18 (5.4)	6 (1.8)	9 (4.5)	4 (2.0)
Decreased appetite	27 (8.1)	8 (2.5)	6 (3.0)	5 (2.5)
Diarrhoea	17 (5.1)	15 (4.6)	10 (5.0)	12 (5.9)
Fatigue	13 (3.9)	13 (4.0)	11 (5.5)	10 (5.0)
Hypokalaemia	20 (6.0)	16 (4.9)	10 (5.0)	10 (5.0)
Malignant neoplasm progression	12 (3.6)	14 (4.3)	7 (3.5)	11 (5.4)
Nausea	37 (11.1)	13 (4.0)	30 (15.1)	11 (5.4)
Neutropenia	45 (13.5)	35 (10.8)	52 (26.1)	37 (18.3)
Neutrophil count decreased	54 (16.2)	46 (14.2)	41 (20.6)	47 (23.3)
Peripheral sensory neuropathy	8 (2.4)	10 (3.1)	4 (2.0)	11 (5.4)
Platelet count decreased	15 (4.5)	16 (4.9)	7 (3.5)	10 (5.0)
Vomiting	38 (11.4)	16 (4.9)	38 (19.1)	9 (4.5)
White blood cell count decreased	8 (2.4)	14 (4.3)	5 (2.5)	11 (5.4)

Race

Table 144: Overview of Safety by Race in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Race = Caucasian		Race = Asian	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 232)	Placebo + mFOLFOX6 or CAPOX (n = 222)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 253)	Placebo + mFOLFOX6 or CAPOX (n = 250)
Any TEAE	**229 (98.7)**	**222 (100.0)**	**253 (100.0)**	**244 (97.6)**
Drug-related TEAE†	225 (97.0)	212 (95.5)	252 (99.6)	237 (94.8)
Zolbetuximab or placebo-related TEAEs†	211 (90.9)	164 (73.9)	232 (91.7)	175 (70.0)
Serious TEAE‡	**119 (51.3)**	**105 (47.3)**	**104 (41.1)**	**108 (43.2)**
Drug-related Serious TEAE†‡	64 (27.6)	40 (18.0)	60 (23.7)	44 (17.6)
Zolbetuximab or placebo-related serious TEAEs†‡	43 (18.5)	26 (11.7)	46 (18.2)	33 (13.2)
TEAE Leading to Death	**24 (10.3)**	**29 (13.1)**	**19 (7.5)**	**20 (8.0)**
TEAE Leading to Permanent Discontinuation of Any Study Drug§	**95 (40.9)**	**74 (33.3)**	**81 (32.0)**	**72 (28.8)**
Drug-related TEAE Leading to Permanent Discontinuation of Any Study Drug†§	75 (32.3)	55 (24.8)	65 (25.7)	52 (20.8)
Drug-related TEAE leading to withdrawal of zolbetuximab or placebo†	29 (12.5)	4 (1.8)	19 (7.5)	11 (4.4)
TEAE Leading to Dose Interruption of Any Study Drug§	**180 (77.6)**	**141 (63.5)**	**190 (75.1)**	**111 (44.4)**
Drug-related TEAE Leading to Dose Interruption of Any Study Drug†§	172 (74.1)	121 (54.5)	173 (68.4)	93 (37.2)
Drug-related TEAE leading to dose interruption of zolbetuximab or placebo†	148 (63.8)	56 (25.2)	104 (41.1)	31 (12.4)
Worst NCI CTCAE ≥ Grade 3 TEAE¶	**195 (84.1)**	**161 (72.5)**	**189 (74.7)**	**180 (72.0)**
Grade 3	141 (60.8)	113 (50.9)	146 (57.7)	134 (53.6)
Grade 4	30 (12.9)	19 (8.6)	24 (9.5)	26 (10.4)
Grade 5	24 (10.3)	29 (13.1)	19 (7.5)	20 (8.0)
Drug-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	162 (69.8)	116 (52.3)	161 (63.6)	132 (52.8)
Grade 3	132 (56.9)	94 (42.3)	137 (54.2)	107 (42.8)
Grade 4	24 (10.3)	16 (7.2)	20 (7.9)	22 (8.8)
Grade 5	6 (2.6)	6 (2.7)	4 (1.6)	3 (1.2)
Zolbetuximab or Placebo-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	117 (50.4)	64 (28.8)	99 (39.1)	70 (28.0)
Grade 3	102 (44.0)	54 (24.3)	87 (34.4)	56 (22.4)
Grade 4	11 (4.7)	8 (3.6)	9 (3.6)	11 (4.4)
Grade 5	4 (1.7)	2 (0.9)	3 (1.2)	3 (1.2)

Table 145: TEAEs ≥ Grade 3 Occurring in ≥ 5% of Participants in Any Treatment Group, by Preferred Term, by Race in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Caucasian		Asian	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 232)	Placebo + mFOLFOX6 or CAPOX (n = 222)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 253)	Placebo + mFOLFOX6 or CAPOX (n = 250)
Any TEAE	**195 (84.1)**	**161 (72.5)**	**189 (74.7)**	**180 (72.0)**
Anaemia	16 (6.9)	17 (7.7)	30 (11.9)	27 (10.8)
Asthenia	14 (6.0)	3 (1.4)	9 (3.6)	6 (2.4)
Decreased appetite	17 (7.3)	2 (0.9)	12 (4.7)	8 (3.2)
Diarrhoea	15 (6.5)	11 (5.0)	9 (3.6)	13 (5.2)
Fatigue	12 (5.2)	10 (4.5)	9 (3.6)	10 (4.0)
Hypertension	9 (3.9)	11 (5.0)	7 (2.8)	2 (0.8)
Hypoalbuminaemia	12 (5.2)	2 (0.9)	5 (2.0)	4 (1.6)
Hypokalaemia	13 (5.6)	12 (5.4)	15 (5.9)	12 (4.8)
Malignant neoplasm progression	5 (2.2)	11 (5.0)	11 (4.3)	11 (4.4)
Nausea	33 (14.2)	9 (4.1)	27 (10.7)	10 (4.0)
Neutropenia	54 (23.3)	44 (19.8)	25 (9.9)	15 (6.0)
Neutrophil count decreased	18 (7.8)	19 (8.6)	69 (27.3)	61 (24.4)
Platelet count decreased	3 (1.3)	4 (1.8)	18 (7.1)	21 (8.4)
Pulmonary embolism	9 (3.9)	14 (6.3)	1 (0.4)	1 (0.4)
Vomiting	42 (18.1)	11 (5.0)	29 (11.5)	9 (3.6)
White blood cell count decreased	2 (0.9)	8 (3.6)	11 (4.3)	16 (6.4)

Region

Table 146: Overview of Safety by Region in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Region = Asia		Region = Non-Asia	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 244)	Placebo + mFOLFOX6 or CAPOX (n = 244)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 289)	Placebo + mFOLFOX6 or CAPOX (n = 283)
Any TEAE	**244 (100.0)**	**238 (97.5)**	**285 (98.6)**	**283 (100.0)**
Drug-related TEAE†	243 (99.6)	231 (94.7)	280 (96.9)	271 (95.8)
Zolbetuximab or placebo-related TEAEs†	223 (91.4)	171 (70.1)	263 (91.0)	213 (75.3)
Serious TEAE‡	**101 (41.4)**	**105 (43.0)**	**144 (49.8)**	**140 (49.5)**
Drug-related Serious TEAE†‡	57 (23.4)	44 (18.0)	77 (26.6)	53 (18.7)
Zolbetuximab or placebo-related serious TEAEs†‡	43 (17.6)	33 (13.5)	54 (18.7)	34 (12.0)
TEAE Leading to Death	**19 (7.8)**	**20 (8.2)**	**30 (10.4)**	**36 (12.7)**
TEAE Leading to Permanent Discontinuation of Any Study Drug§	**79 (32.4)**	**69 (28.3)**	**120 (41.5)**	**100 (35.3)**
Drug-related TEAE Leading to Permanent Discontinuation of Any Study Drug†§	63 (25.8)	49 (20.1)	98 (33.9)	72 (25.4)
Drug-related TEAE leading to withdrawal of zolbetuximab or placebo†	17 (7.0)	11 (4.5)	39 (13.5)	6 (2.1)
TEAE Leading to Dose Interruption of Any Study Drug§	**181 (74.2)**	**108 (44.3)**	**228 (78.9)**	**176 (62.2)**
Drug-related TEAE Leading to Dose Interruption of Any Study Drug†§	164 (67.2)	91 (37.3)	218 (75.4)	145 (51.2)
Drug-related TEAE leading to dose interruption of zolbetuximab or placebo†	98 (40.2)	31 (12.7)	186 (64.4)	64 (22.6)
Worst NCI CTCAE ≥ Grade 3 TEAE¶	**181 (74.2)**	**174 (71.3)**	**246 (85.1)**	**216 (76.3)**
Grade 3	141 (57.8)	129 (52.9)	179 (61.9)	150 (53.0)
Grade 4	21 (8.6)	25 (10.2)	37 (12.8)	30 (10.6)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Region = Asia		Region = Non-Asia	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 244)	Placebo + mFOLFOX6 or CAPOX (n = 244)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 289)	Placebo + mFOLFOX6 or CAPOX (n = 283)
Grade 5	19 (7.8)	20 (8.2)	30 (10.4)	36 (12.7)
Drug-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	154 (63.1)	127 (52.0)	209 (72.3)	160 (56.5)
Grade 3	133 (54.5)	103 (42.2)	170 (58.8)	129 (45.6)
Grade 4	17 (7.0)	21 (8.6)	32 (11.1)	23 (8.1)
Grade 5	4 (1.6)	3 (1.2)	7 (2.4)	8 (2.8)
Zolbetuximab or placebo-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	94 (38.5)	69 (28.3)	153 (52.9)	85 (30.0)
Grade 3	83 (34.0)	55 (22.5)	133 (46.0)	69 (24.4)
Grade 4	8 (3.3)	11 (4.5)	15 (5.2)	13 (4.6)
Grade 5	3 (1.2)	3 (1.2)	5 (1.7)	3 (1.1)

Table 147: TEAEs ≥ Grade 3 Occurring in ≥ 5% of Participants in Any Treatment Group, by Preferred Term, by Region in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Asia		Non-Asia	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 244)	Placebo + mFOLFOX6 or CAPOX (n = 244)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 289)	Placebo + mFOLFOX6 or CAPOX (n = 283)
Any TEAE	**181 (74.2)**	**174 (71.3)**	**246 (85.1)**	**216 (76.3)**
Anaemia	29 (11.9)	26 (10.7)	22 (7.6)	28 (9.9)
Asthenia	9 (3.7)	6 (2.5)	18 (6.2)	4 (1.4)
Decreased appetite	12 (4.9)	8 (3.3)	21 (7.3)	5 (1.8)
Diarrhoea	9 (3.7)	13 (5.3)	18 (6.2)	14 (4.9)
Fatigue	9 (3.7)	9 (3.7)	15 (5.2)	14 (4.9)
Hypoalbuminaemia	4 (1.6)	3 (1.2)	15 (5.2)	3 (1.1)
Hypokalaemia	15 (6.1)	11 (4.5)	15 (5.2)	15 (5.3)
Nausea	24 (9.8)	9 (3.7)	43 (14.9)	15 (5.3)
Neutropenia	22 (9.0)	13 (5.3)	75 (26.0)	59 (20.8)
Neutrophil count decreased	68 (27.9)	59 (24.2)	27 (9.3)	34 (12.0)
Peripheral sensory neuropathy	5 (2.0)	3 (1.2)	7 (2.4)	18 (6.4)
Platelet count decreased	18 (7.4)	21 (8.6)	4 (1.4)	5 (1.8)
Vomiting	27 (11.1)	8 (3.3)	49 (17.0)	17 (6.0)
White blood cell count decreased	11 (4.5)	15 (6.1)	2 (0.7)	10 (3.5)

Gastrectomy status

Table 148: Overview of Safety by Gastrectomy Status in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Gastrectomy Status = Yes		Gastrectomy Status = No	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 159)	Placebo + mFOLFOX6 or CAPOX (n = 156)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 374)	Placebo + mFOLFOX6 or CAPOX (n = 371)
Any TEAE	**157 (98.7)**	**156 (100.0)**	**372 (99.5)**	**365 (98.4)**
Drug-related TEAE†	156 (98.1)	155 (99.4)	367 (98.1)	347 (93.5)
Zolbetuximab or placebo-related TEAEs†	139 (87.4)	117 (75.0)	347 (92.8)	267 (72.0)
Serious TEAE‡	**66 (41.5)**	**71 (45.5)**	**179 (47.9)**	**174 (46.9)**
Drug-related Serious TEAE†‡	32 (20.1)	26 (16.7)	102 (27.3)	71 (19.1)

Category, n (%)	Integrated SPOTLIGHT/GLOW			
	Gastrectomy Status = Yes		Gastrectomy Status = No	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 159)	Placebo + mFOLFOX6 or CAPOX (n = 156)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 374)	Placebo + mFOLFOX6 or CAPOX (n = 371)
Zolbetuximab or placebo-related serious TEAEs†‡	27 (17.0)	18 (11.5)	70 (18.7)	49 (13.2)
TEAE Leading to Death	**7 (4.4)**	**9 (5.8)**	**42 (11.2)**	**47 (12.7)**
TEAE Leading to Permanent Discontinuation of Any Study Drug§	**55 (34.6)**	**50 (32.1)**	**144 (38.5)**	**119 (32.1)**
Drug-related TEAE Leading to Permanent Discontinuation of Any Study Drug†§	49 (30.8)	40 (25.6)	112 (29.9)	81 (21.8)
Drug-related TEAE leading to withdrawal of zolbetuximab or placebo†	12 (7.5)	5 (3.2)	44 (11.8)	12 (3.2)
TEAE Leading to Dose Interruption of Any Study Drug§	**119 (74.8)**	**89 (57.1)**	**290 (77.5)**	**195 (52.6)**
Drug-related TEAE Leading to Dose Interruption of Any Study Drug†§	105 (66.0)	73 (46.8)	277 (74.1)	163 (43.9)
Drug-related TEAE leading to dose interruption of zolbetuximab or placebo†	62 (39.0)	22 (14.1)	222 (59.4)	73 (19.7)
Worst NCI-CTCAE ≥ Grade 3 TEAE¶	**122 (76.7)**	**116 (74.4)**	**305 (81.6)**	**274 (73.9)**
Grade 3	95 (59.7)	93 (59.6)	225 (60.2)	186 (50.1)
Grade 4	20 (12.6)	14 (9.0)	38 (10.2)	41 (11.1)
Grade 5	7 (4.4)	9 (5.8)	42 (11.2)	47 (12.7)
Drug-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	106 (66.7)	84 (53.8)	257 (68.7)	203 (54.7)
Grade 3	86 (54.1)	69 (44.2)	217 (58.0)	163 (43.9)
Grade 4	19 (11.9)	14 (9.0)	30 (8.0)	30 (8.1)
Grade 5	1 (0.6)	1 (0.6)	10 (2.7)	10 (2.7)
Zolbetuximab or placebo-related Worst NCI CTCAE Grade TEAE ≥ Grade 3 †¶	68 (42.8)	45 (28.8)	179 (47.9)	109 (29.4)
Grade 3	57 (35.8)	38 (24.4)	159 (42.5)	86 (23.2)
Grade 4	10 (6.3)	6 (3.8)	13 (3.5)	18 (4.9)
Grade 5	1 (0.6)	1 (0.6)	7 (1.9)	5 (1.3)

Table 149: TEAEs ≥ Grade 3 Occurring in ≥ 5% of Participants in Any Treatment Group, by System Organ Class and Preferred Term, by Gastrectomy Subgroup in the Integrated Analysis of SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	History of Gastrectomy		No History of Gastrectomy	
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 159)	Placebo + mFOLFOX6 or CAPOX (n = 156)	Zolbetuximab + mFOLFOX6 or CAPOX (n = 374)	Placebo + mFOLFOX6 or CAPOX (n = 371)
Any TEAE	**122 (76.7)**	**116 (74.4)**	**305 (81.6)**	**274 (73.9)**
Blood and lymphatic system disorders	**40 (25.2)**	**41 (26.3)**	**109 (29.1)**	**93 (25.1)**
Neutropenia	28 (17.6)	20 (12.8)	69 (18.4)	52 (14.0)
Anaemia	12 (7.5)	17 (10.9)	39 (10.4)	37 (10.0)
Gastrointestinal disorders	**38 (23.9)**	**34 (21.8)**	**135 (36.1)**	**81 (21.8)**
Nausea	15 (9.4)	5 (3.2)	52 (13.9)	19 (5.1)
Vomiting	14 (8.8)	5 (3.2)	62 (16.6)	20 (5.4)
Diarrhoea	5 (3.1)	10 (6.4)	22 (5.9)	17 (4.6)
General disorders and administration site conditions	**26 (16.4)**	**17 (10.9)**	**45 (12.0)**	**33 (8.9)**
Asthenia	15 (9.4)	4 (2.6)	12 (3.2)	6 (1.6)
Fatigue	5 (3.1)	8 (5.1)	19 (5.1)	15 (4.0)
Investigations	**52 (32.7)**	**44 (28.2)**	**97 (25.9)**	**94 (25.3)**
Neutrophil count decreased	34 (21.4)	35 (22.4)	61 (16.3)	58 (15.6)
Platelet count decreased	10 (6.3)	4 (2.6)	12 (3.2)	22 (5.9)
Metabolism and nutrition disorders	**35 (22.0)**	**27 (17.3)**	**69 (18.4)**	**38 (10.2)**

Hypokalaemia	13 (8.2)	13 (8.3)	17 (4.5)	13 (3.5)
Decreased appetite	11 (6.9)	6 (3.8)	22 (5.9)	7 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**5 (3.1)**	**7 (4.5)**	**19 (5.1)**	**27 (7.3)**
Malignant neoplasm progression	4 (2.5)	6 (3.8)	15 (4.0)	19 (5.1)

Table 150: Differences in Demographics and Baseline Disease Characteristics by Gastrectomy Status in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

	Integrated SPOTLIGHT/GLOW			
	History of Gastrectomy		No History of Gastrectomy	
Parameter Category/Statistic	**Zolbetuximab + mFOLFOX6 or CAPOX (n = 159)**	**Placebo + mFOLFOX6 or CAPOX (n = 156)**	**Zolbetuximab + mFOLFOX6 or CAPOX (n = 374)**	**Placebo + mFOLFOX6 or CAPOX (n = 371)**
Race, n (%)				
Caucasian	61 (39.4)	57 (38.0)	171 (48.3)	165 (48.1)
Black or African American	0	0	5 (1.4)	1 (0.3)
Asian	89 (57.4)	90 (60.0)	164 (46.3)	160 (46.6)
American Indian or Alaska Native	1 (0.6)	1 (0.7)	7 (2.0)	7 (2.0)
Other	4 (2.6)	2 (1.3)	7 (2.0)	10 (2.9)
Missing	4	6	20	28
Medical Condition, n (%)				
Gastric adenocarcinoma	137 (86.2)	129 (82.7)	297 (79.4)	285 (76.8)
Gastro-oesophageal junction adenocarcinoma	22 (13.8)	27 (17.3)	77 (20.6)	86 (23.2)
Tumour Metastatic				
No	53 (33.3)	57 (36.5)	23 (6.1)	17 (4.6)
Yes	106 (66.7)	99 (63.5)	351 (93.9)	354 (95.4)

2.6.8.8. Immunological events

Please refer to section 2.6.2 "Clinical pharmacology".

2.6.8.9. Safety related to drug-drug interactions and other interactions

Zolbetuximab is a humanized monoclonal antibody which is cleared from the circulation through protein catabolism. Therefore, formal pharmacokinetic interaction studies have not been conducted. Since monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of zolbetuximab.

The impact of concomitant administration of chemotherapy components on the exposure of zolbetuximab and vice versa was investigated in Study ILUSTRO. The exposure (Cmax and AUCtau) of zolbetuximab was generally comparable when co-administered with mFOLFOX6 compared with zolbetuximab administered alone. Co-administration of zolbetuximab with oxaliplatin appeared to slightly increase total platinum and free platinum exposure (by about 10% to 16%) and increase Cmax of free platinum (by about 30%) but not total platinum. Concomitant administration of zolbetuximab with 5-FU did not affect the systemic exposure of 5-FU.

2.6.8.10. Discontinuation due to adverse events

Table 151: TEAEs Leading to Permanent Discontinuation of Zolbetuximab or Placebo Occurring in > 1 Participant in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)		Placebo + mFOLFOX6 or CAPOX (n = 527)	
	All	Related	All	Related
TEAE Leading to Permanent Discontinuation of Zolbetuximab or Placebo	**106 (19.9)**	**56 (10.5)**	**66 (12.5)**	**17 (3.2)**
Blood and Lymphatic System Disorders	**5 (0.9)**	**2 (0.4)**	**3 (0.6)**	**2 (0.4)**
Disseminated intravascular coagulation	2 (0.4)	1 (0.2)	0	0
Anaemia	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)
Cardiac Disorders	**4 (0.8)**	**3 (0.6)**	**4 (0.8)**	**2 (0.4)**
Acute myocardial infarction	2 (0.4)	2 (0.4)	1 (0.2)	0
Cardiac arrest	0	0	2 (0.4)	2 (0.4)
Gastrointestinal Disorders	**46 (8.6)**	**28 (5.3)**	**17 (3.2)**	**6 (1.1)**
Vomiting	20 (3.8)	19 (3.6)	3 (0.6)	1 (0.2)
Nausea	18 (3.4)	16 (3.0)	2 (0.4)	1 (0.2)
Upper gastrointestinal haemorrhage	4 (0.8)	1 (0.2)	2 (0.4)	1 (0.2)
Diarrhoea	3 (0.6)	0	1 (0.2)	0
Dysphagia	3 (0.6)	0	2 (0.4)	0
Intestinal obstruction	3 (0.6)	1 (0.2)	0	0
Abdominal pain	2 (0.4)	1 (0.2)	0	0
Obstruction gastric	2 (0.4)	1 (0.2)	0	0
Haematemesis	0	0	2 (0.4)	1 (0.2)
General Disorders and Administration Site Conditions	**14 (2.6)**	**9 (1.7)**	**6 (1.1)**	**3 (0.6)**
Malaise	4 (0.8)	4 (0.8)	0	0
Fatigue	3 (0.6)	2 (0.4)	0	0
Asthenia	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Chest discomfort	2 (0.4)	2 (0.4)	0	0
Death	2 (0.4)	0	1 (0.2)	1 (0.2)
Immune System Disorders	**2 (0.4)**	**2 (0.4)**	**1 (0.2)**	**0**
Anaphylactic reaction	2 (0.4)	2 (0.4)	0	0
Infections and Infestations	**10 (1.9)**	**3 (0.6)**	**10 (1.9)**	**1 (0.2)**
Pneumonia	5 (0.9)	1 (0.2)	2 (0.4)	0
Septic shock	1 (0.2)	0	2 (0.4)	1 (0.2)
Injury, Poisoning and Procedural Complications	**4 (0.8)**	**2 (0.4)**	**0**	**0**
Infusion related reaction	2 (0.4)	2 (0.4)	0	0
Investigations	**10 (1.9)**	**5 (0.9)**	**5 (0.9)**	**1 (0.2)**
Blood bilirubin increased	2 (0.4)	0	1 (0.2)	0
Gamma-glutamyltransferase increased	2 (0.4)	0	0	0
Platelet count decreased	2 (0.4)	2 (0.4)	0	0
Weight decreased	2 (0.4)	0	0	0
Aspartate aminotransferase increased	1 (0.2)	0	2 (0.4)	0
Ejection fraction decreased	0	0	2 (0.4)	1 (0.2)
Metabolism and Nutrition Disorders	**9 (1.7)**	**5 (0.9)**	**4 (0.8)**	**2 (0.4)**
Decreased appetite	4 (0.8)	4 (0.8)	0	0
Hypokalaemia	2 (0.4)	1 (0.2)	0	0

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)		Placebo + mFOLFOX6 or CAPOX (n = 527)	
	All	Related	All	Related
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	**7 (1.3)**	**0**	**11 (2.1)**	**1 (0.2)**
Malignant neoplasm progression	6 (1.1)	0	6 (1.1)	0
Metastases to meninges	1 (0.2)	0	2 (0.4)	0
Tumour haemorrhage	0	0	2 (0.4)	1 (0.2)
Nervous System Disorders	**7 (1.3)**	**4 (0.8)**	**5 (0.9)**	**1 (0.2)**
Intracranial pressure increased	2 (0.4)	0	0	0
Renal and Urinary Disorders	**3 (0.6)**	**2 (0.4)**	**3 (0.6)**	**0**
Acute kidney injury	1 (0.2)	1 (0.2)	2 (0.4)	0
Respiratory, Thoracic and Mediastinal Disorders	**4 (0.8)**	**2 (0.4)**	**7 (1.3)**	**1 (0.2)**
Acute respiratory distress syndrome	0	0	2 (0.4)	0
Pleural effusion	0	0	3 (0.6)	1 (0.2)
Vascular Disorders	**4 (0.8)**	**3 (0.6)**	**0**	**0**
Flushing	2 (0.4)	2 (0.4)	0	0

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

Table 152: TEAEs Leading to Dose Interruption of Zolbetuximab or Placebo Occurring in > 2 Participants in Any Treatment Group in the SPOTLIGHT and GLOW Studies (Safety Analysis Set)

MedDRA v25.0 System Organ Class Preferred Term, n (%)	Integrated SPOTLIGHT/GLOW			
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)		Placebo + mFOLFOX6 or CAPOX (n = 527)	
	All	Related	All	Related
TEAE Leading to Dose Interruption of Zolbetuximab or Placebo	**348 (65.3)**	**284 (53.3)**	**182 (34.5)**	**95 (18.0)**
Blood and Lymphatic System Disorders	**77 (14.4)**	**43 (8.1)**	**76 (14.4)**	**42 (8.0)**
Neutropenia	60 (11.3)	30 (5.6)	51 (9.7)	28 (5.3)
Anaemia	13 (2.4)	8 (1.5)	14 (2.7)	7 (1.3)
Thrombocytopenia	12 (2.3)	9 (1.7)	19 (3.6)	13 (2.5)
Leukopenia	4 (0.8)	2 (0.4)	2 (0.4)	0
Gastrointestinal Disorders	**225 (42.2)**	**213 (40.0)**	**26 (4.9)**	**14 (2.7)**
Vomiting	150 (28.1)	147 (27.6)	9 (1.7)	6 (1.1)
Nausea	147 (27.6)	143 (26.8)	5 (0.9)	3 (0.6)
Abdominal pain	23 (4.3)	22 (4.1)	3 (0.6)	2 (0.4)
Abdominal pain upper	18 (3.4)	14 (2.6)	0	0
Diarrhoea	8 (1.5)	4 (0.8)	9 (1.7)	4 (0.8)
Dyspepsia	6 (1.1)	6 (1.1)	0	0
Upper gastrointestinal haemorrhage	6 (1.1)	6 (1.1)	2 (0.4)	2 (0.4)
Salivary hypersecretion	4 (0.8)	4 (0.8)	1 (0.2)	0
Intestinal obstruction	3 (0.6)	1 (0.2)	0	0
Retching	3 (0.6)	3 (0.6)	0	0
General Disorders and Administration Site Conditions	**70 (13.1)**	**43 (8.1)**	**20 (3.8)**	**12 (2.3)**
Chills	13 (2.4)	12 (2.3)	0	0
Fatigue	13 (2.4)	7 (1.3)	11 (2.1)	7 (1.3)
Asthenia	12 (2.3)	4 (0.8)	3 (0.6)	2 (0.4)
Pyrexia	11 (2.1)	4 (0.8)	4 (0.8)	2 (0.4)

MedDRA v25.0 System Organ Class	Integrated SPOTLIGHT/GLOW			
	Zolbetuximab + mFOLFOX6 or CAPOX (n = 533)		Placebo + mFOLFOX6 or CAPOX (n = 527)	
Preferred Term, n (%)	All	Related	All	Related
Malaise	6 (1.1)	6 (1.1)	0	0
Non-cardiac chest pain	6 (1.1)	5 (0.9)	0	0
Chest discomfort	5 (0.9)	5 (0.9)	0	0
Chest pain	3 (0.6)	3 (0.6)	0	0
Oedema peripheral	3 (0.6)	1 (0.2)	0	0
Hepatobiliary Disorders	**1 (0.2)**	**0**	**10 (1.9)**	**3 (0.6)**
Hepatotoxicity	0	0	3 (0.6)	0
Hyperbilirubinaemia	0	0	3 (0.6)	1 (0.2)
Infections and Infestations	**31 (5.8)**	**1 (0.2)**	**23 (4.4)**	**4 (0.8)**
COVID-19	8 (1.5)	0	11 (2.1)	0
Herpes zoster	0	0	3 (0.6)	1 (0.2)
Injury, Poisoning and Procedural Complications	**14 (2.6)**	**11 (2.1)**	**4 (0.8)**	**1 (0.2)**
Infusion related reaction	7 (1.3)	7 (1.3)	0	0
Investigations	**67 (12.6)**	**33 (6.2)**	**66 (12.5)**	**31 (5.9)**
Neutrophil count decreased	33 (6.2)	14 (2.6)	33 (6.3)	12 (2.3)
Platelet count decreased	13 (2.4)	9 (1.7)	22 (4.2)	14 (2.7)
Aspartate aminotransferase increased	7 (1.3)	4 (0.8)	9 (1.7)	6 (1.1)
Alanine aminotransferase increased	6 (1.1)	3 (0.6)	9 (1.7)	4 (0.8)
Blood bilirubin increased	5 (0.9)	0	2 (0.4)	2 (0.4)
White blood cell count decreased	5 (0.9)	2 (0.4)	7 (1.3)	3 (0.6)
Blood pressure increased	3 (0.6)	3 (0.6)	0	0
Blood alkaline phosphatase increased	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)
Metabolism and Nutrition Disorders	**21 (3.9)**	**11 (2.1)**	**15 (2.8)**	**7 (1.3)**
Decreased appetite	8 (1.5)	6 (1.1)	2 (0.4)	0
Hypokalaemia	6 (1.1)	4 (0.8)	4 (0.8)	2 (0.4)
Musculoskeletal and Connective Tissue Disorders	**6 (1.1)**	**3 (0.6)**	**4 (0.8)**	**2 (0.4)**
Back pain	3 (0.6)	3 (0.6)	1 (0.2)	0
Nervous System Disorders	**25 (4.7)**	**15 (2.8)**	**9 (1.7)**	**1 (0.2)**
Headache	8 (1.5)	6 (1.1)	2 (0.4)	0
Dizziness	6 (1.1)	3 (0.6)	1 (0.2)	0
Respiratory, Thoracic and Mediastinal Disorders	**16 (3.0)**	**10 (1.9)**	**14 (2.7)**	**4 (0.8)**
Cough	5 (0.9)	4 (0.8)	1 (0.2)	0
Dyspnoea	5 (0.9)	3 (0.6)	3 (0.6)	1 (0.2)
Pulmonary embolism	0	0	3 (0.6)	1 (0.2)
Skin and Subcutaneous Tissue Disorders	**19 (3.6)**	**12 (2.3)**	**9 (1.7)**	**2 (0.4)**
Hyperhidrosis	5 (0.9)	5 (0.9)	0	0
Palmar-plantar erythrodysaesthesia syndrome	4 (0.8)	1 (0.2)	5 (0.9)	1 (0.2)
Erythema	3 (0.6)	3 (0.6)	0	0
Vascular Disorders	**36 (6.8)**	**31 (5.8)**	**6 (1.1)**	**1 (0.2)**
Hypertension	17 (3.2)	16 (3.0)	2 (0.4)	0
Flushing	6 (1.1)	6 (1.1)	0	0
Hypotension	6 (1.1)	4 (0.8)	4 (0.8)	1 (0.2)
Hot flush	3 (0.6)	3 (0.6)	0	0

Data cutoff dates were as follows: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022.

2.6.8.11. Post marketing experience

Zolbetuximab was granted marketing authorization in Japan on 26 March 2024.

2.6.9. Discussion on clinical safety

The safety data supporting the MAA of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of CLDN18.2-positive gastric or GEJ adenocarcinoma are derived from the two pivotal randomized, double-blind, placebo-controlled phase 3 studies SPOTLIGHT and GLOW. The integrated safety analysis of SPOTLIGHT and GLOW includes safety data from 533 patients in the zolbetuximab + mFOLFOX6 or CAPOX arm (=combined phase 3 zolbetuximab group) and 527 patients in the placebo + mFOLFOX6 or CAPOX arm (=combined phase 3 control group).

Overall, the safety database is deemed sufficient to adequately characterize the toxicity profile of zolbetuximab in combination with chemotherapy. In order to gain the most comprehensive information on safety, pooled safety data for zolbetuximab at the intended posology (800/600 mg/m^2 Q3W) in combination with chemotherapy from studies FAST, ILUSTRO, SPOTLIGHT and GLOW were requested. Compared to the previous integrated safety analysis of SPOTLIGHT and GLOW, the newly provided safety data based on the integrated phase 2 and phase 3 analysis (Zolbetuximab + EOX/mFOLFOX6/CAPOX: N=631, EOX or PBO + mFOLFOX6/CAPOX: N=611) did not reveal meaningful differences and thus, did not alter previous conclusions drawn on the safety of zolbetuximab. As requested, the pooled phase 2 and phase 3 data were however used for re-evaluation and selection of ADRs to be presented in the SmPC.

No clinical safety data are available for the additional posology claim of 800/400 mg/m² Q2W. Any data provided are solely based on population PK and exposure-response modelling.

Patient exposure

Referring to the integrated analysis of SPOTLIGHT and GLOW, the median duration of exposure to zolbetuximab or placebo was 171.0 days in the zolbetuximab plus mFOLFOX6 arm and 173.0 days in the placebo plus mFOLFOX6 arm and thus comparable. The number of patients exposed to treatment for > 48 weeks is rather low. However, given that at the time of data cutoff only 16.8% of patients were still on treatment with zolbetuximab + mFOLFOX6 in SPOTLIGHT and 11.8% of patients were still on treatment with zolbetuximab + CAPOX in GLOW, it is not anticipated that safety data would change tremendously and therefore, no update of safety data is currently requested.

Relative dose intensity and number of oxaliplatin infusions and fluoropyrimidine cycles administered in both studies seem comparable between both treatment arms, indicating that co-administration of did not significantly impact the tolerability to chemotherapy.

Adverse events-

According to the integrated analysis of safety of SPOTLIGHT and GLOW, the **most frequent TEAEs** (> 20%) by PT were nausea (75.8% vs. 55.8%), vomiting (66.8% vs. 33.4%), decreased appetite (44.3% vs. 33.6%), anaemia (35.6% vs. 37.0%), diarrhoea (35.6% vs. 39.5%), neutrophil count decreased (31.0% vs. 28.5%), peripheral sensory neuropathy (30.4% vs. 33.0%), neutropenia (28.5% vs. 24.5%), constipation (25.9% vs. 31.1%), fatigue (21.0% vs. 25.2%), AST increased (21.0% vs. 22.0%), abdominal pain (20.1% vs. 25.8%), asthenia (20.1% vs. 18.2%) and platelet count decreased (18.9% vs. 20.7%). TEAEs reported with a ≥ 10% higher incidence in the combined phase 3 zolbetuximab group than in the combined phase 3 control group were nausea (+20%), vomiting (+33.4%) and decreased appetite (+10.7%). Besides, peripheral oedema and hypoalbuminaemia were experienced more frequently in the combined phase 3 zolbetuximab group than in the combined phase 3 control group (peripheral oedema: 14.1 vs. 6.1%; hypoalbuminaemia: 18.8% vs. 9.9%). A tendency towards an increased occurrence of vascular disorders is apparent in the combined phase 3 zolbetuximab group as compared to the combined phase 3 control group (24.4% vs.

17.8%), of which the PT of hypertension was reported as most common TEAE also being more frequent in the combined phase 3 zolbetuximab group as compared to the combined phase 3 control group (8.6% vs. 5.5%). Increased incidences of thrombotic events in the combined zolbetuximab as compared to the combined control group are obvious in all TEAE categories presented (see Table 126, Table 127, Table 128). However, there are a variety of factors, such as the underlying disease and other medical conditions, that may have contributed to or may have confounded the rates of thrombosis/embolism events. Thus, a clear causal relationship between the occurrence of thrombotic events and treatment with zolbetuximab is currently not suggested.

The **most frequent TEAEs considered by the investigator to be related to zolbetuximab or placebo** generally resemble the most frequent TEAEs that occurred regardless of treatment relationship. TEAEs considered by the investigator to be related to zolbetuximab or placebo reported with a ≥ 5% higher incidence in the combined phase 3 zolbetuximab group than in the combined phase 3 control group were mainly gastrointestinal disorders such as nausea (64.9% vs. 36.1%), vomiting (59.1% vs. 16.5%), and decreased appetite (26.5% vs. 19.9%). Furthermore, hypertension was reported as TEAE considered by the investigator to be related to zolbetuximab or placebo with a ≥ 5% higher incidence in the combined phase 3 zolbetuximab group than in the combined phase 3 control group (6.8% vs. 0.9%).

Referring to the data on any drug-related TEAEs, zolbetuximab- or placebo-related TEAEs and chemotherapy-related TEAEs, it is suggested that no clear attribution of TEAE causality was possible and the majority of TEAEs was considered by the investigator to be related to the combination of zolbetuximab + chemotherapy, and not specifically to zolbetuximab/placebo or chemotherapy. It was finally clarified that within the rates of zolbetuximab- or placebo-related TEAEs, participants are included who had TEAEs related to both zolbetuximab or chemotherapy.

Grade ≥ 3 TEAEs were more common in the zolbetuximab + CT arms than in the placebo + CT arms (80.1% in the combined phase 3 zolbetuximab group vs. 74.0% in the combined phase 3 control group), while the difference was even more pronounced in **grade ≥ 3 TEAEs that were considered to be related to zolbetuximab or placebo** by the investigator (46.3% in the combined phase 3 zolbetuximab group vs. 29.2% in the combined phase 3 control group). Most common grade ≥ 3 TEAEs (all-cause and zolbetuximab/placebo-related) were neutropenia, neutrophil count decreased, vomiting, and nausea. Grade ≥ 3 vomiting and nausea (all-cause and zolbetuximab/placebo-related) were reported with a ≥ 5% higher incidence in the combined phase 3 zolbetuximab group than in the combined phase 3 control group (all-cause vomiting: 14.3% vs. 4.7%, all-cause nausea: 12.6% vs. 4.6; zolbetuximab- or placebo-related vomiting: 11.8% vs. 1.7%, zolbetuximab- or placebo-related nausea: 9.9% vs. 1.9%).

The incidence of **serious adverse events** was similar between the zolbetuximab + CT treatment arms and the placebo + CT treatment arms (46.0% participants in the combined phase 3 zolbetuximab group and 46.5% participants in the combined phase 3 control group). By far the most SAEs were observed in the SOC of gastrointestinal disorders (20.5% in the combined phase 3 zolbetuximab group and 17.5% in the combined phase 3 control group). The most frequent SAEs by PT were vomiting (7.1% vs. 4.6%), nausea (5.6% vs. 3.2%) and malignant neoplasm progression (3.6% vs. 4.7%). **SAEs considered as zolbetuximab- or placebo-related** were slightly more common in in the combined phase 3 zolbetuximab group than in the combined phase 3 control group (18.2% vs. 12.7%). Relevant differences between the combined phase 3 zolbetuximab group and the combined phase 3 control group were again observed in the SOC of gastrointestinal disorders (vomiting: 5.1% vs. 1.1% and nausea: 4.1% vs. 1.1%. Among the reported SAEs, there were further some cases of upper gastrointestinal haemorrhage, intestinal obstruction, ascites, and ileus, which were reported with a higher incidence in the combined phase 3 zolbetuximab group compared to the control group (for both all-cause and considered related to zolbetuximab/placebo). This data confirms that the complete

SOC of gastrointestinal disorders, including some life-threatening conditions, is highly affected by zolbetuximab toxicity.

The overall incidence of **deaths due to TEAEs** was similar between the zolbetuximab + CT treatment arms and the placebo +CT treatment arms (9.2% of deaths in the combined phase 3 zolbetuximab group and 10.6% of deaths in the combined phase 3 control group). The most frequently reported TEAE leading to death was malignant neoplasm progression, which was observed in 3.0% of patients in the combined phase 3 zolbetuximab group and 4.7% of patients in the combined phase 3 control group. The higher rate in the combined phase 3 control group may be explained by the treatment effect of zolbetuximab. Any other TEAEs by PT resulting in death were reported with frequencies <1%. **Zolbetuximab- or placebo-related TEAEs leading to death** were reported at low frequencies and were comparable between treatment groups (1.5% of participants in the combined phase 3 zolbetuximab group and 1.1% of participants in the combined phase 3 control group).

TEAEs leading to permanent discontinuation of at least one component of any study drug were reported in 37.3% of participants in the combined phase 3 zolbetuximab group and 32.1% of participants in the combined phase 3 control group. TEAEs leading to permanent discontinuation of zolbetuximab or placebo were reported in 19.9% of participants in the combined phase 3 zolbetuximab group and 12.5% of participants in the combined phase 3 control group, of whom 10.5% in the combined phase 3 zolbetuximab group and 3.2% in the combined phase 3 control group were considered to be **related to zolbetuximab or placebo**. Vomiting and nausea were identified to be the major contributors to the reported rates of treatment discontinuations due to TEAEs.

TEAEs leading to dose interruption for at least one component of any study drug were 76.7% of participants in the combined phase 3 zolbetuximab group and 53.9% of participants in the combined phase 3 control group. Regarding zolbetuximab/placebo dose interruptions, a remarkable higher incidence was reported for the combined phase 3 zolbetuximab group compared to the control group (65.3% vs. 34.5% for all TEAEs and 53.3% s. 18.0% for related TEAEs). Once again, the SOC where higher differences were reported between treatment groups was gastrointestinal disorders, with 42.2% vs. 4.9% reported incidence for all TEAEs and 40.0% vs. 2.7% for related TEAEs, which further substantiates the severe gastrointestinal toxicity of zolbetuximab.

Adverse events of special interest (AESIs)

Based on observations during the clinical development of zolbetuximab, the group terms "Nausea", "Vomiting", "Abdominal Pain", "Hypersensitivity Reactions", "IRRs", "Anaemia" and "Neutropenia" were considered **adverse events of special interest (AESIs)**. For these events, an integrated analysis was performed in which additional PTs were added to form a pooled group term.

Nausea, vomiting, abdominal pain

These analyses were equal or highly comparable to the findings from previous analyses, given that the AESI "nausea" solely consisted of the PT nausea and the AESI "vomiting" consisted of the PTs vomiting, vomiting projectile, retching and cyclic vomiting syndrome. Of note, in most participants with "nausea" and "vomiting" events, the first event occurred within the first 21 days after the start of the first infusion in cycle 1: Based on the integrated analysis of phase 2 and phase 3 studies, the onset of nausea was between Day ≥1 to <22 in 64.0% of patients in the combined zolbetuximab group vs. 40.6% of patients in the combined control group. Onset of vomiting was between Day ≥1 to <22 in 52.1% of patients in the combined zolbetuximab group vs. 19.3% of patients in the combined control group. However, about 20% or more patients experienced an onset of nausea or vomiting in the combined zolbetuximab group up to cycle 4. Moreover, higher rates of nausea and vomiting were reported for the combined zolbetuximab group as compared to the combined control group nearly

throughout the complete course of treatment, indicating that gastrointestinal toxicity of zolbetuximab in combination with chemotherapy is increased during the whole treatment period (see also Figure 24

Figure 27)

The majority of nausea and vomiting events were experienced during the day or 1 day after the infusions. In patients treated with zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy, the median duration of nausea and vomiting was 3 days and 1 day. This has now been reflected in the SmPC.

Prior to treatment with zolbetuximab in combination with fluoropyrimidine and platinum containing chemotherapy, prescribers should evaluate the individual patient's risk of gastrointestinal toxicities. It is important to proactively manage nausea and vomiting to mitigate the potential risk of reduced exposure to zolbetuximab and/or chemotherapy.

To prevent nausea and vomiting, pre-treatment with a combination of antiemetics is recommended prior to each infusion of zolbetuximab. During infusion, patients should be closely monitored and toxicities managed by infusion interruption and/or infusion rate reduction to minimize the risk of severe adverse reactions or early treatment discontinuation.

During and after infusion, patients should be monitored and managed using standard of care, including antiemetics or fluid replacement, as clinically indicated.

Nausea and vomiting should be managed according dose modifications as recommended in section 4.2 of the SmPC).
The group term "abdominal pain" comprised the PTs of abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, abdominal distension, abdominal symptom, abdominal tenderness, gastrointestinal pain and epigastric discomfort. No major differences were observed in the incidence of "abdominal pain" events between the combined phase 3 zolbetuximab and combined phase 3 control group (34.0% vs 36.4%).

Hypersensitivity reactions

Hypersensitivity reactions based on SMQ (broad) were reported in 35.8% and 32.2% of participants in the combined phase 3 zolbetuximab group and the combined phase 3 control group, respectively. Grade ≥ 3 "hypersensitivity reaction" events were reported in 27 participants (5.1%) in the combined phase 3 zolbetuximab group and 13 participants (2.5%) in the combined phase 3 control group. A serious event of "hypersensitivity reaction" was experienced by 19 (3.6%) participants in the combined phase 3 zolbetuximab group and 8 (1.5%) participants in the combined phase 3 control group.

For description in section 4.4 and 4.8 of the SmPC, solely the two PTs drug hypersensitivity and anaphylactic reaction were selected from the list of hypersensitivity reactions based on SMQ broad.

Patients should be monitored during and after infusion with zolbetuximab (at least 2 hours, or longer if clinically indicated) for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (urticaria, repetitive cough, wheeze and throat tightness/change in voice).

Hypersensitivity reactions should be managed according to the dose modifications as recommended in Table 2 of the SmPC.

Infusion-related Reactions (flagged by Investigators)

Infusion-related reactions (assessed by investigator) were reported in 40.3% and 11.0% of participants in the combined phase 3 zolbetuximab group and the combined phase 3 control group, respectively. Grade ≥ 3 infusion-related reactions (assessed by investigator) were reported in 37 participants (7.0%) in the combined phase 3 zolbetuximab group and 3 participants (0.6%) in the

combined phase 3 control group. A serious event of investigator-assessed IRRs was experienced by 17 (3.2%) participants in the combined phase 3 zolbetuximab group and no participants in the combined phase 3 control group. It was clarified that IRRs were defined as events occurring during the infusion or within 1 day of the infusion with symptoms such as nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough and hypertension. TEAEs flagged by the investigator as "infusion-related reaction" were additionally assessed as individual TEAEs occurring during the trial. Of note, solely the isolated PT "infusion-related reaction" was selected from the list of IRRs assessed by investigator (grouped term) to be reflected in the SmPC.

Patients should be monitored for signs and symptoms of infusion-related reactions including nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough, and hypertension. These signs and symptoms are usually reversible with the interruption of the infusion.

Infusion-related reactions should be managed according to the dose modifications as recommended in Table 2 of the SmPC.

Anemia

The group term "anemia" was derived from the hematopoietic erythropenia SMQ broad. No considerable differences in the incidence of anemia events were observed between the combined phase 3 zolbetuximab group (36.0%) and the combined phase 3 control group (37.2%).

Neutropenia

The group term neutropenia comprised the PTs febrile neutropenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased and neutropenic colitis. Slightly higher incidences of neutropenia events were reported in patients treated with zolbetuximab + CT: "neutropenia" events (any grade) in 57.2% vs. 52.0%, grade ≥ 3 events of "neutropenia" in 35.9% vs. 31.5%, and SAEs of "neutropenia" in 3.9% vs. 2.8% of participants in the combined phase 3 zolbetuximab group and the combined phase 3 control group.

Adverse drug reactions

The **integrated phase 2 and phase 3 analysis** was the basis for the identification of ADRs.

Re-evaluation of ADRs applying above stricter quantitative criteria was requested which led to the identification of ADRs that were still not considered to reflect the entire safety profile of zolbetuximab. For instance, the Applicant did not see any causal relationship between events of pyrexia, hypertension, chills, and weight decreased and the treatment with zolbetuximab. Inclusion of these PTs as ADRs for zolbetuximab was again requested, given that a causal, even if indirect, relationship with the treatment with zolbetuximab was apparent, instance, weight decrease naturally results from vomiting, nausea and decreased appetite. Similarly, if IRRs are established as ADR for zolbetuximab, the accompanying symptoms (such as pyrexia, hypertension, chills) would analogously be considered related to the study treatment. The Applicant finally agreed to also include the respective events in the list of ADRs reported in section 4.8 of the SmPC.

Cardiac electrophysiology

Analyses of cardiac electrophysiology based on SPOTLIGHT and GLOW revealed cases of QTcF intervals > 450 msec, however no relevant differences between treatment groups were identified (32.1% vs. 32.5% in the combined zolbetuximab group vs. control group). Change from baseline of > 60 msec was reported in 15.3% subjects from the combined phase 3 zolbetuximab treatment group and 13.2% subjects in the control group. As no dedicated QT-study was conducted to fully exclude an impact of zolbetuximab on cardiac electrophysiology, and zolbetuximab is given in combination with

chemotherapy, for which QT prolongation events are known to occur, monitoring of cardiac toxicities as conducted in routine clinical practice is important.

Safety in special populations

Age

For the analysed age categories (≤ 65 years vs. > 65 years, ≤ 75 years and > 75 years), no consistent trend in the incidence of TEAEs throughout the different TEAE categories was apparent. Safety data for patients who are > 75 years of age are limited, which is adequately reflected in the SmPC**.**

Sex

Female participants are expected to achieve slightly higher zolbetuximab exposure (plasma concentrations) than male participants, resulting in a higher probability to experience TEAEs leading to dose interruption and TEAEs ≥ Grade 3. Specifically, grade ≥ 3 nausea and vomiting were experienced more frequently in female participants as compared to male participants in the combined phase 3 zolbetuximab group, while the incidences were similar between female and male participants in the combined phase 3 control group. However, there was no difference in the drug exposure of zolbetuximab between female and male participants in terms of cumulative actual dose, relative dose intensity, and number of infusions administered. It is also expected that TEAEs are appropriately managed without impact on the exposure of the backbone treatment and that patients are appropriately followed (see also discussion on clinical safety). Consequently, it is anticipated that female patients are equally able to complete zolbetuximab treatments and derive benefit and no specific dose adjustments are warranted.

Race/Region

TEAEs leading to discontinuation or dose interruption of zolbetuximab or placebo and TEAEs ≥ grade 3 were more common in Caucasian as compared to Asian participants in the combined phase 3 zolbetuximab group, while differences were not or to a lesser extent observed in the combined phase 3 placebo group. The same trend was observed for grade ≥ 3 TEAEs by region.

Similar to the overall population, GI disorders (nausea and vomiting) were among the PTs that mainly contributed to higher grade ≥3 TEAE rates reported in Caucasian vs. Asian and Asia vs. Non-Asia subgroups. Of note, the difference of the incidence of grade ≥ 3 TEAEs of nausea and vomiting in Caucasian/Non-Asian patients was larger in the zolbetuximab as compared to the control group. No differences were however observed in all-cause or drug-related nausea and vomiting events comparing the Caucasian and Asian or Non-Asian and Asian population.

Higher rates of dose interruptions and treatment discontinuations of zolbetuximab in the Caucasian vs. Asian subgroup finally led to a reduced exposure of zolbetuximab regarding the duration of treatment, cumulative actual dose and relative dose intensity. This resulted in reduced efficacy of zolbetuximab + chemotherapy (see also discussion on clinical efficacy).

Gastrectomy status

Serious TEAEs, TEAEs leading to death, and TEAEs ≥ grade 3 were slightly more common in patients without gastrectomy as compared to patients with gastrectomy in the combined phase 3 zolbetuximab group. Amongst others, the higher incidence of TEAEs in patients without gastrectomy vs. patients with gastrectomy result from gastrointestinal toxicities: The incidence of TEAEs with PT nausea and vomiting was significantly higher in patients without gastrectomy in the combined zolbetuximab group, while the incidence of nausea and vomiting in the control group was similar or even lower in patients without gastrectomy vs. patients with gastrectomy. These findings are suggested to relate to the mode of action of zolbetuximab and the presence or absence of the target cells in the stomach, respectively.

Referring to the demographics and baseline disease characteristics presented by gastrectomy status, it is further noted that some imbalances may also have contributed to the differences observed in TEAE rates between patients with and without gastrectomy. For instance, less participants were Caucasian (~39%) in the subgroup of patients with gastrectomy as compared to patients without gastrectomy (~48%). Given that higher TEAE incidences have also been demonstrated in the Caucasian population, there might have been some overlapping contribution to the effects observed within subgroups. Similarly, the subgroup of patients without gastrectomy was comprised of less patients diagnosed with gastric adenocarcinoma but more patients with GEJ adenocarcinoma. Furthermore, nearly all patients were metastatic in the subgroup of patients without gastrectomy, while the subgroup of patients with gastrectomy was comprised of solely 2/3 of patients with metastatic tumours. These imbalances may have confounded the subgroup analyses by gastrectomy status and no definite conclusions may be drawn at this point.

Additional expert consultation

According to EURACAN, the most relevant side effects that may limit the use of zolbetuximab are nausea and vomiting, which were also experienced as grade ≥ 3 TEAEs in a considerable number of patients. Special attention would be needed "to manage these toxicities with an intensification of support care treatment in primary prevention". Finally, it was considered that the impact of nausea and vomiting on patient quality of life "must be formally evaluated".

2.6.10. Conclusions on clinical safety

The most frequent and severe toxicities related to the treatment of zolbetuximab in combination with chemotherapy are gastrointestinal disorders such as nausea and vomiting. In order to limit the impact on the quality of life of patients and the tolerability of other standard treatment with chemotherapy, extensive warnings and precautions as risk mitigation measures have been implemented in the SmPC to optimize the toxicity management and improve the tolerability in clinical practice. Furthermore, these events most frequently occur during the early course of treatment and are acceptable in the context of advanced or metastatic gastric or GEJ cancer.

2.7. Risk management plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

There are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection proposed for zolbetuximab.

2.7.3. Risk minimisation measures

Safety concern	Routine risk minimisation activities
None	Not applicable

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.03.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vyloy (zolbetuximab) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

The approved indication is:

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

Gastric cancer is the fifth most common cancer in the world. Expected median survival for unresectable advanced or metastatic HER2-negative gastric/GEJ cancer with currently available standard of care is around 1 year with a 5-year relative survival rate of only 6%. The treatment aim is palliative. (Morgan et al, 2022; Sung et al, 2021)

3.1.2. Available therapies and unmet medical need

Currently recommended first-line therapies for locally advanced unresectable or metastatic disease include fluoropyrimidine- and platinum backbone (containing cisplatin or oxaliplatin and 5-FU or capecitabine) in combination with therapy depending on HER2 and PD-L1 CPS status. [Ajani et al, 2022; Lordick et al, 2022]:

Recently, nivolumab and pembrolizumab were approved in the combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of HER2-negative advanced or metastatic gastric or GEJ adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5 or CPS ≥1, respectively.

3.1.3. Main clinical studies

Two global, randomized, double-blind and placebo-controlled phase 3 studies evaluated zolbetuximab in combination with fluoropyrimidine- and platinum containing chemotherapy as first line treatment in participants with locally advanced unresectable or metastatic HER2 negative gastric or GEJ adenocarcinoma whose tumours were CLDN18.2-positive.

CLDN18.2-positive tumours were defined as ≥ 75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining based on central IHC assessment using the investigational VENTANA CLDN18 (43-14A) RxDx Assay.

Participants in the SPOTLIGHT study received zolbetuximab or placebo in combination with mFOLFOX6 (n=565); the GLOW study evaluated zolbetuximab plus CAPOX compared with placebo plus CAPOX (n=507).

The dose of zolbetuximab that was used in both pivotal studies were 800 mg/m² as a single loading dose followed by 600 mg/m² every three weeks.

The primary endpoint was PFS assessed by IRC, with OS as key secondary endpoint.

3.2. Favourable effects

Both pivotal studies SPOTLIGHT and GLOW demonstrated statistically significant improvements in the primary endpoint PFS (assessed by IRC per RECIST v1.1) and the key secondary endpoint of OS (final PFS and IA OS analyses).

Study SPOTLIGHT

A PFS HR of 0.75 (95% CI: 0.598, 0.94; p-value 0.0066) was reported for the comparison of the zolbetuximab arm versus the control arm (median PFS 10.6 vs 8.7 months, 10.1% difference in PFS rate at 18 months).

The survival benefit was based on a stratified HR of 0.75 (95% CI: 0.60, 0.94; p-value 0.0053) with a difference in median OS of 2.7 months (median OS 18.2 vs 15.5 months, 12.4% difference in OS rate at 18 months in the zolbetuximab vs the control group.

Exploratory endpoints of time to progression (TTP) and PFS2 supported a benefit for the addition of zolbetuximab; median time to date of progressive disease was delayed by 5.3 months; the difference in median PFS2 was 2.2 months between the zolbetuximab treatment group and the control group (PFS2 HR 0.78; 95% CI 0.64, 0.96).

The OS and PFS benefit were confirmed with updated data (based on cutoff for final OS analyses, see effects table).

Study GLOW

A PFS improvement was observed for zolbetuximab plus CAPOX compared to placebo plus CAPOX: PFS HR 0.69 (95% CI 0.54, 0.87; p-value 0.0007; median PFS 8.2 vs 6.8 months, 13.3% difference in PFS rate at 18 months).

OS data resulted in an OS HR of 0.77 (95% CI 0.62, 0.965; p-value 0.0118; median OS 14.4 vs 12.2 months, 10% difference in OS rates at 18 months) for the comparison of the zolbetuximab vs the placebo arm.

As in SPOTLIGHT, exploratory endpoints of time to progression (TTP) and PFS2 supported a benefit for the addition of zolbetuximab; median time to date of progressive disease was delayed by 3.7 months; the difference in median PFS2 was 2 months between the zolbetuximab treatment arm and the control arm (PFS2 HR 0.71; 95% CI 0.58, 0.87).

The PFS and OS benefit was sustained with updated data at the time of the final OS analyses, see effects table.

3.3. Uncertainties and limitations about favourable effects

Both pivotal studies showed a marginal PFS and OS benefit in the large subgroup of Caucasian participants (45% of all study participants): PFS and OS HR 0.92 [95% CI 0.73, 1.2] (for comparison PFS HR 0.56 [95% CI 0.44, 0.7] and OS HR 0.64 [95% CI 0.51, 0.8] in Asian participants) (see section 5.1 of the SmPC). Additional analyses overall support the hypothesis that the lower exposure due to discontinuations/dose interruptions could be the main factor for the observed lower treatment effect in the Caucasian subgroup. Additional warnings and precautions as risk mitigations measures have been implemented in the SmPC (section 4.4) to optimize the toxicity management and improve the tolerability and treatment effect in clinical practice and therefore mitigating the potential risk of reduced exposure to zolbetuximab and/or chemotherapy (in both GC and GEJ).

The observed effect in PFS and OS is not supported by secondary endpoints of ORR, DOR or PRO data. The additional key secondary endpoint "time to first confirmed deterioration" (TTCD) of physical function, OG25-Pain and GHS/QoL showed no meaningful differences between treatment arms. ORR and DOR by IRC based on unconfirmed responses and mean scores of other HRQoL measures were similar between the zolbetuximab treatment groups and the control groups.
Only a limited number of patients were recruited with an age ≥ 75 years, this has been reflected in the SmPC.

3.4. Unfavourable effects

The incidence of treatment-emergent adverse events was higher in the combined phase 3 zolbetuximab group than in the combined phase 3 control group in the following TEAE categories:

- zolbetuximab- or placebo-related TEAEs (91.2% vs. 72.9%)
- all-cause and zolbetuximab- or placebo-related grade ≥ 3 TEAEs (80.1% vs. 74.0% and 46.3% vs. 29.2%)
- zolbetuximab- or placebo-related SAEs (18.2% vs. 12.7%)
- all-cause and drug-related TEAEs leading to treatment discontinuation of any study drug (37.3% vs. 32.1% and 30.2% vs. 23.0%)
- all-cause and drug-related TEAEs leading to dose interruption of any study drug (76.7% vs. 53.9% and 71.7% vs. 44.8%)

Similar frequencies in both treatment groups were reported for all-cause SAEs (46.0% vs 46.5%) and all-cause TEAEs leading to death (9.2% vs 10.6%).

Most common zolbetuximab- or placebo-related TEAEs in the combined phase 3 zolbetuximab group were nausea (64.9%), vomiting (59.1%), decreased appetite (26.5%), neutrophil count decreased (15.8%), neutropenia (14.3%).

Nausea and vomiting were the most common grade ≥ 3 TEAEs and SAEs with considerably higher incidence in the combined phase 3 zolbetuximab group as compared to the combined phase 3 control group:

- all-cause and zolbetuximab- or placebo-related grade ≥ 3 nausea (12.6% vs. 4.6% and 9.9% vs. 1.9%)
- all-cause and zolbetuximab- or placebo-related SAE of nausea (5.6% vs. 3.2% and 4.1% vs. 1.1%)
- all-cause and zolbetuximab- or placebo-related grade ≥ 3 vomiting (14.3% vs. 4.7% and 11.8% vs. 1.7%)
- all-cause and zolbetuximab- or placebo-related SAE of vomiting (7.1% vs. 4.6% and 5.1% vs. 1.1%)

Nausea and vomiting led to discontinuation of any study drug in 3.4% and 3.8% of patients in the combined phase 3 zolbetuximab group. Nausea and vomiting leading to dose interruption of any study drug were experienced by 27.6% and 28.1% of patients in the combined phase 3 zolbetuximab group.

3.5. Uncertainties and limitations about unfavourable effects

The safety database for patients aged > 75 years is limited. This is reflected in the SmPC.

TEAEs leading to discontinuation or interruption of study drug and TEAEs grade ≥ 3 were more common in Caucasian participants as compared to Asian participants and in participants from the Non-Asian as compared to Asian region. Additional risk mitigation measures have been implemented in the SmPC to optimize the toxicity management and improve the tolerability in clinical practice.

3.6. Effects Table

Table 153: Effects Table for Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy for 1L treatment of locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN 18.2 positive (data cut-off: 15-Nov-2023 for study SPOTLIGHT and 12-Jan-2024 for study GLOW)

Effect	Short Description	Unit	Zolbetuximab + mFOLFOX6 or CAPOX (N=533)	Placebo + mFOLFOX6 or CAPOX (N=527)	Uncertainties/ Strength of evidence	Ref
Favourable Effects in study SPOTLIGHT (backbone mFOLFOX6) (final OS, updated PFS; DCO 08 Sep 2023)						
PFS, median	Based on IRC per RECIST 1.1	months	11.0	8.9	Primary endpoint PFS is statistically significant (p-value 0.0066); difference in median PFS 2.1 months; 12.2% diff. in PFS rate at 18 months; prespecified sensitivity analyses consistent with primary analysis; OS key secondary endpoint, results statistically significant (p-value 0.0053); difference in median OS 2.6 months, 12.4% diff. in OS rate at 18 months;	
		HR, (95% CI)	**0.73** (0.591, 0.910)			
OS, median	Time from randomization until death	months	18.2	15.6		
		HR, (95% CI)	**0.78** (0.64, 0.95)			
Favourable Effects in study GLOW (backbone CAPOX) (final OS, updated PFS analyses; DCO 12 Jan 2024)						
PFS, median	Based on IRC per RECIST 1.1	months	8.2	6.8	Primary endpoint PFS is statistically significant (p-value 0.0007); difference in median PFS 1.4 months; 11.2% diff. in PFS rate at 18 months; prespecified sensitivity analyses consistent with primary analysis;	
		HR, (95% CI)	**0.69** (0.55, 0.86)			
OS, median	Time from randomization until death	months	14.3	12.2	OS key secondary endpoint, results statistically significant (p-value 0.0118); difference in median OS 2.1 months, 11.3% diff. in OS rate at 18 months;	
		HR, (95% CI)	0.76 (0.62, 0.94)			
					Uncertainties: Lower treatment effect in Caucasian	
Unfavourable Effects in integrated analysis across studies SPOTLIGHT and GLOW (DCO SPOTLIGHT: 08 Sep 2023; DCO GLOW: 12 Jan 2024)						
Tolerability						

Effect	Short Description	Unit	Zolbetuximab + mFOLFOX6 or CAPOX (N=533)	Placebo + mFOLFOX6 or CAPOX (N=527)	Uncertainties/ Strength of evidence	Ref
	Grade ≥3 AE **Z/P related**	**%**	80.1 **46.3**	74.0 **29.2**		
	Serious AE **Z/P related**	%	46.0 **18.2**	46.5 **12.7**		
	AE leading to death **Z/P related**	%	9.2 **1.5**	10.6 **1.1**	• Limited database for patients older than 75. • Higher TEAE rates in Caucasian/Non-Asian as compared to Asian study population.	SCS Table 6
	AE leading to permanent discont. **drug related**	%	37.3 **30.2**	32.1 **23.0**		
	AE leading to interrupt. **drug related**	%	76.7 **71.7**	53.9 **44.8**		
Nausea	**All-cause** Grade ≥ 3 Serious	**%**	**75.8** 12.6 5.6	**55.8** 4.6 3.2		SCS Table 7 SCS Table 8 SCS Table 9 SCS Table 11
Vomiting	**All-cause** Grade ≥ 3 Serious	%	**66.8** 14.3 7.1	**33.4** 4.7 4.6		

Abbreviations: Z/P = zolbetuximab or placebo, discount. = discontinuation, interrupt. = interruption, DCO: data cutoff date

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy analysis of the two pivotal studies SPOTLIGHT and GLOW demonstrated statistically significant improvements in PFS and OS that can be considered clinically meaningful to support a benefit for the addition of zolbetuximab to standard 1L chemotherapy in advanced GEJ/gastric cancer in the overall study population (which included ~50% of participants from Asian countries).

The mainly gastrointestinal toxicities such as nausea and vomiting were most frequently experienced during the early course of treatment and generally, is considered acceptable in the proposed indication of advanced or metastatic gastric or GEJ cancer.

3.7.2. Balance of benefits and risks

The reported survival improvement in this palliative setting is considered to outweigh the observed gastrointestinal toxicities that are associated with the addition of zolbetuximab to standard chemotherapy.

Exploratory subgroup analyses of efficacy for SPOTLIGHT and GLOW showed a lower treatment effect in terms of PFS and OS for Caucasian versus Asian subjects (as reflected in section 5.1 of the SmPC). Additional analyses support the hypothesis that a lower exposure due to discontinuations/dose interruptions could be the main factor for the observed lower treatment effect in the Caucasian subgroup. Higher rates of discontinuations/interruptions in Caucasian were attributed to AEs, primarily nausea and vomiting. Additional warnings and precautions as risk mitigation measures have been implemented in the SmPC to optimize the toxicity management and improve the tolerability in clinical practice and therefore address the potential risk of reduced exposure to zolbetuximab and/or chemotherapy (in both GC and GEJ) in this patient subgroup.

3.7.3. Additional considerations on the benefit-risk balance

The Applicant seeks approval of an alternative dosage regimen of 800 mg/m² as loading dose followed by 400 mg/m² every 2 weeks that has not been evaluated yet in any clinical study. The application of the second dose is based on PK modelling only. Several attempts were made to improve the pop PK model which did not fully address the concerns towards the predictiveness of the final pop PK model. It is however agreed that both regimens are expected to achieve similar benefit-risk profiles. Based on the totality of evidence and given that the clinically untested regimen is expected to achieve exposure ranges fully covered by the Q3W regimen and observed during the clinical development, the alternative Q2W regimen, more convenient for patients receiving combination therapy following the same dosing interval, is deemed acceptable.

3.8. Conclusions

The overall benefit/risk balance of Vyloy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP recommends by a majority of 28 out of 29 votes that the benefit-risk balance of Vyloy is favourable in the following indication(s):

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 4.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Zolbetuximab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Divergent position

Divergent position to the majority recommendation is appended to this report.

5. Appendix

5.1. Divergent position dated 25 July 2024

APPENDIX

DIVERGENT POSITION DATED 25 July 2024

DIVERGENT POSITION DATED 25 July 2024

Vyloy EMEA/H/C/005868/0000

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Vyloy indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours are Claudin 18.2 positive (see section 5.1).

The reason for divergent opinion was the following:

While (pooled) results from the pivotal studies suggest relatively small overall survival benefit, we do not consider that the benefits outweigh the risks in this palliative setting. The toxicity observed impacts quality of life and possibly also the ability to tolerate standard treatment with chemotherapy; thereby, harming patients and necessitating intensive premedication. To us, this weighs strong in the benefit-risk assessment. Furthermore, it is unclear what the benefit of therapy will be in the EU population. Note that subgroup analyses indicate no PFS/OS benefit in the subset of Caucasian patients – a common demographic in the EU. This finding is thought/hypothesized to be the result of lower zolbetuximab exposure due to discontinuations/dose interruptions (i.e., tolerability issues). Therefore, we consider the B/R of zolbetuximab in this indication negative.

Peter Mol NL