Summary Report of Benefit-Risk Assessment

VYLOY™ POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 100MG/VIAL

NEW DRUG APPLICATION

Active Ingredient	Zolbetuximab
Product Registrant	Astellas Pharma Singapore Pte. Ltd.
Product Registration Number	SIN17197P
Application Route	Full evaluation
Date of Approval	06 March 2025

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A INTRODUCTION

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.

The active substance, zolbetuximab, is a first-in-class monoclonal antibody directed against the tight junction molecule CLDN18.2. After binding to CLDN18.2, zolbetuximab stimulates cellular and soluble immune effectors that activate antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, thereby initiates an anti-tumour immune response. Preclinical and early phase clinical studies demonstrated improved anti-tumour activity when zolbetuximab is given in combination with chemotherapy as compared to monotherapy.

Vyloy is available as a powder for concentrate for solution for infusion containing 100 mg of zolbetuximab per vial. The excipients are arginine, phosphoric acid, sucrose and polysorbate 80.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, zolbetuximab, is manufactured at [redacted]
The drug product, Vyloy, is manufactured at Baxter Oncology GmbH, [redacted] Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits were considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is [redacted] The stability data presented was adequate to support the storage of the drug substance at ≤ -60°C with a shelf-life period of 48 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted on three consecutive production-scale batches. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B guideline and impurity limits were considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is a 20 mL Clear Type I glass vial with grey bromobutyl rubber stopper, aluminium seal with a green cap. The stability data submitted was adequate to support the approved shelf-life of 48 months when stored between 2-8°C. Once reconstituted with water for injection, the solution may be stored at room temperature (not more than 30°C) for up to 6 hours.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of HER2-negative and CLDN18.2-positive locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma was based primarily on two similarly designed Phase III studies SPOTLIGHT and GLOW. In both studies, CLDN18.2 positivity of the tumour (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining) was confirmed by immunohistochemistry with the validated Ventana CLDN18 (43-14A) RxDx assay performed in a central laboratory.

SPOTLIGHT

This was a Phase III, randomised, double-blind study of add-on zolbetuximab to mFOLFOX6 in patients with HER2-negative and CLDN18.2-positive locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma that had not been previously treated with systemic chemotherapy in this setting. mFOLFOX6 comprises oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, 5-fluorouracil 400 mg/m^2 given as a bolus and 5-fluorouracil 2400 mg/m^2 given as a continuous infusion

Patients were randomised 1:1 to receive zolbetuximab in combination with mFOLFOX6 or placebo in combination with mFOLFOX6, stratified according to region (Asia vs non-Asia), number of organs with metastases (0 to 2 vs ≥3) and previous gastrectomy (yes vs no).

Zolbetuximab was administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by a subsequent dose of 600 mg/m^2 every 3 weeks in combination with up to 12 treatments (4 cycles) of mFOLFOX6 administered on Days 1, 15 and 29 of a 42-day cycle. After 12 treatments, patients were allowed to continue treatment with zolbetuximab, 5-

fluorouracil and folinic acid (leucovorin or local equivalent) at the discretion of the investigator, until progression of disease or unacceptable toxicity. Antiemetic premedication was administered prior to each treatment according to institutional standard of care and published guidelines. This included neurokinin-1 (NK-1) receptor blockers and 5-hydroxytryptamine type 3 (5-HT3) receptor blockers.

Treatment with zolbetuximab continued until RECIST v1.1-defined progression of disease as determined by an independent review committee (IRC), or a subsequent anticancer treatment was initiated. Tumour assessments were performed every 9 weeks up to and including week 54, then every 12 weeks thereafter.

The primary efficacy endpoint was progression-free survival (PFS) as assessed per RECIST v1.1 by an IRC, which was planned when 300 patients had disease progression or died. The key secondary endpoint was overall survival (OS).

A total of 565 patients were randomised: 283 patients to zolbetuximab plus mFOLFOX6 and 282 patients to placebo plus mFOLFOX6 arm. As of the data cut-off date (DCO) of 09 Sep 2022, the median duration of exposure to zolbetuximab/placebo was 190 days in the add-on zolbetuximab arm and 195 days in the mFOLFOX6 arm. The median duration of all components administered (127 days vs 130 days) as well as the proportion of patients who completed 24 weeks of mFOLFOX6 treatment were similar between both treatment arms (36.9% vs 35.6%).

The patient demographics and baseline disease characteristics were generally well balanced between the treatment arms. The median age was 61 years (range 20 to 86 years), with 64.1% aged 65 years or younger. Most patients were White (53.3%) or Asian (37.5%), with an ECOG performance status of 1 (56.7%) or 0 (43.1%). The majority of the study population had gastric cancer (75.9%) while 24.1% had GEJ adenocarcinoma. Additionally, most of the patients presented with metastatic disease at baseline (84.4%).

At the primary analysis (DCO of 09 Sep 2022), a statistically significant increase in PFS of 1.9 months was demonstrated in the zolbetuximab plus mFOLFOX arm over the mFOLFOX6 arm. The median PFS per IRC was 10.61 (95% confidence interval [CI]: 8.90, 12.48) months in the add-on zolbetuximab arm and 8.67 (95% CI: 8.21, 10.28) months in the mFOLFOX6 arm (hazard ratio [HR] 0.751; 95% CI: 0.598, 0.942; one-sided p=0.0066). Results from the subgroup analyses for region (Asia vs non-Asia) (HR 0.563 vs 0.848), number of metastatic sites (0 to 2 vs ≥3) (HR 0.726 vs 0.844) and previous gastrectomy (yes vs no) (HR 0.622 vs 0.808) were consistent with those observed in the primary analysis.

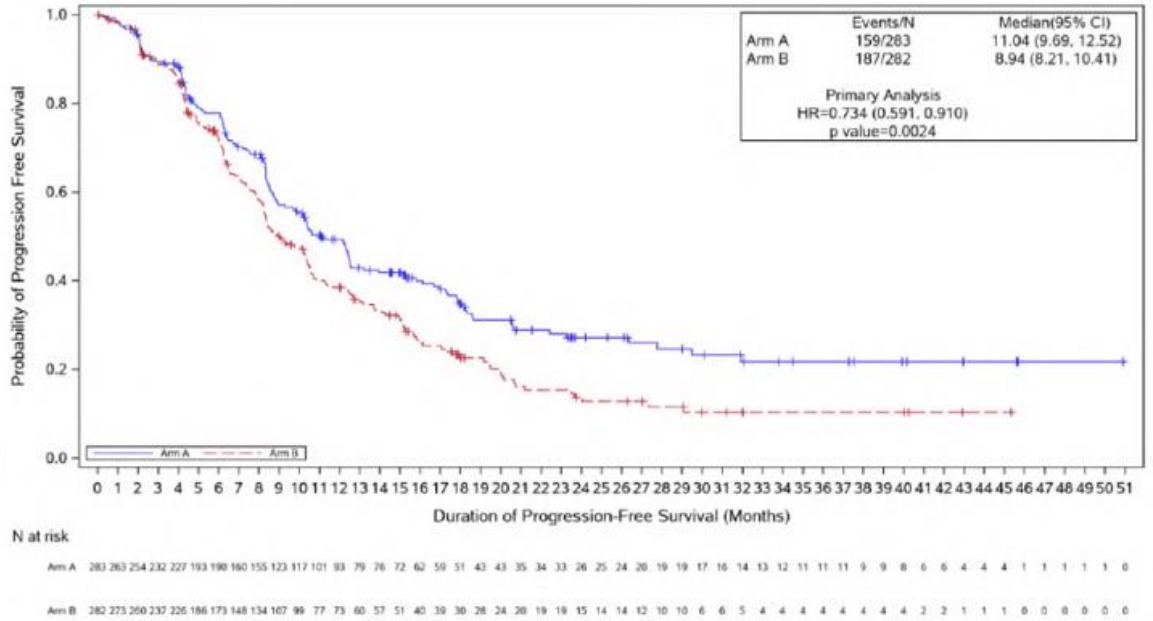
In the final analysis (DCO of 08 Sep 2023), add-on zolbetuximab resulted in an increase in PFS of 2.1 months as compared to the mFOLFOX6 arm, which was consistent with the primary analysis.

SPOTLIGHT: PFS as assessed by IRC

PFS	**Primary analysis DCO: 09 Sep 2022**		**Final analysis DCO: 08 Sep 2023**	
	Zolbetuximab + mFOLFOX6 (N=283)	**Placebo + mFOLFOX6 (N=282)**	**Zolbetuximab + mFOLFOX6 (N=283)**	**Placebo + mFOLFOX6 (N=282)**
PFS events, n (%)	146 (51.6)	167 (59.2)	159 (56.2)	187 (66.3)
Median, months (95% CI)	10.61 (8.90, 12.48)	8.67 (8.21, 10.28)	11.04 (9.69, 12.52)	8.94 (8.21, 10.41)

HR (95% CI) One-sided p-value	0.751 (0.598, 0.942) 0.0066		0.734 (0.591, 0.910) 0.0024	
Median follow-up time, months (95% CI)	12.94 (11.63, 15.28)	12.65 (10.71, 15.24)	18.04 (15.28, 23.33)	17.91 (14.78, 23.75)
12-month PFS (%) (95% CI)	48.86 (41.92, 55.43)	35.04 (28.45, 41.69)	49.28 (42.62, 55.60)	38.47 (32.08, 44.81)
24-month PFS (%) (95% CI)	24.41 (17.36, 32.13)	14.87 (8.78, 22.47)	27.20 (20.75, 34.03)	13.66 (8.74, 19.66)

SPOTLIGHT: Kaplan-Meier plot of PFS assessed by IRC, final analysis



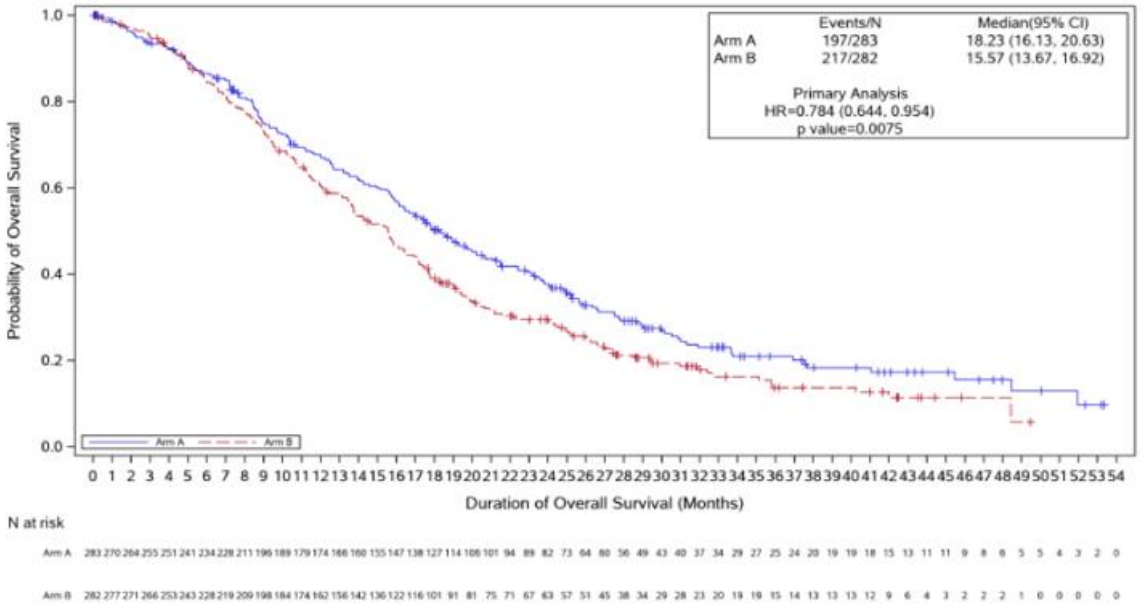
Arm A: Zolbetuximab + mFOLFOX6; Arm B: Placebo + mFOLFOX6

The key secondary endpoint of OS showed a statistically significant improvement of 2.7 months for the zolbetuximab combination compared to mFOLFOX6 at the primary analysis. The median OS was 18.23 (95% CI: 16.43, 22.90) months in the zolbetuximab arm and 15.54 (95% CI: 13.47, 16.53) months in the mFOLFOX6 arm (HR 0.750; 95% CI: 0.601, 0.936; one-sided p=0.0053). The survival benefit was maintained at 2.7 months at the final analysis.

SPOTLIGHT: OS results

OS	**Primary analysis DCO: 09 Sep 2022**		**Final analysis DCO: 08 Sep 2023**	
	Zolbetuximab + mFOLFOX6 (N=283)	**Placebo + mFOLFOX6 (N=282)**	**Zolbetuximab + mFOLFOX6 (N=283)**	**Placebo + mFOLFOX6 (N=282)**
No of events, n (%)	149 (52.7)	177 (62.8)	197 (69.6)	217 (77.0)
Median, months (95% CI)	18.23 (16.43, 22.90)	15.54 (13.47, 16.53)	18.23 (16.13, 20.63)	15.57 (13.67, 16.92)
HR (95% CI) One-sided p-value	0.750 (0.601, 0.936) 0.0053		0.784 (0.644, 0.954) 0.0075	
Median follow-up time, months (95% CI)	22.14 (18.04, 24.77)	20.93 (19.61, 25.66)	33.28 (29.27, 37.59)	31.38 (28.68, 36.17)
12-month OS (%) (95% CI)	67.69 (61.49, 73.12)	59.97 (53.63, 65.72)	67.36 (61.36, 72.64)	60.65 (54.57, 66.19)
24-month OS (%) (95% CI)	38.77 (31.62, 45.85)	28.38 (22.10, 34.98)	37.71 (31.68, 43.71)	29.45 (23.99, 35.10)

SPOTLIGHT: Kaplan-Meier plot of OS, final analysis



Arm A: Zolbetuximab + mFOLFOX6; Arm B: Placebo + mFOLFOX6

GLOW

This was a Phase III, randomised, double-blind study of add-on zolbetuximab to CAPOX in patients with HER2-negative and CLDN.18.2-positive locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma that had not been previously treated with systemic chemotherapy in this setting. CAPOX consists of oxaliplatin 130 mg/m^2 administered on Day 1 and capecitabine 1000 mg/m^2 on Days 1 to 14 of a 21-day cycle.

Patients were randomised 1:1 to receive zolbetuximab in combination with CAPOX or placebo in combination with CAPOX, stratified according to region (Asia vs non-Asia), number of organs with metastases (0 to 2 vs ≥3) and previous gastrectomy (yes vs no).

The dosing regimen used for zolbetuximab is the same as that in SPOTLIGHT (loading dose of 800 mg/m^2 on Day 1 of cycle 1 followed by a subsequent dose of 600 mg/m^2 every 3 weeks). Patients received up to 8 treatments of CAPOX. After 8 treatments of oxaliplatin, patients were allowed to continue treatment of zolbetuximab and capecitabine at the discretion of the investigator, until progression of disease or unacceptable toxicity.

The study design and endpoints for this study were identical to those in study SPOTLIGHT, except that the doublet chemotherapy used was the CAPOX regimen.

A total of 507 patients were randomised: 254 patients to zolbetuximab plus CAPOX and 253 patients to placebo plus CAPOX arm. As of the DCO of 07 Oct 2022, the median duration of exposure to zolbetuximab/placebo was 134 days in the add-on zolbetuximab arm and 148 days in the CAPOX arm. The median duration of all components administered (119 days vs 118 days), as well as the proportion of patients who completed 24 weeks of CAPOX treatment were similar between both treatment arms (27.6% vs 27.7%).

The patient demographics and baseline disease characteristics were generally well-balanced between the treatment arms. The median age was 60 years (range 21 to 83 years), with 70.2% aged 65 years or younger. Most patients were Asian (63.2%) or White (36.8%), with an ECOG

performance status of 1 (57.1%) or 0 (42.9%). The majority of the study population had gastric cancer (84.4%) while 15.6% had GEJ adenocarcinoma. Additionally, most of the patients presented with metastatic disease at baseline (87.6%).

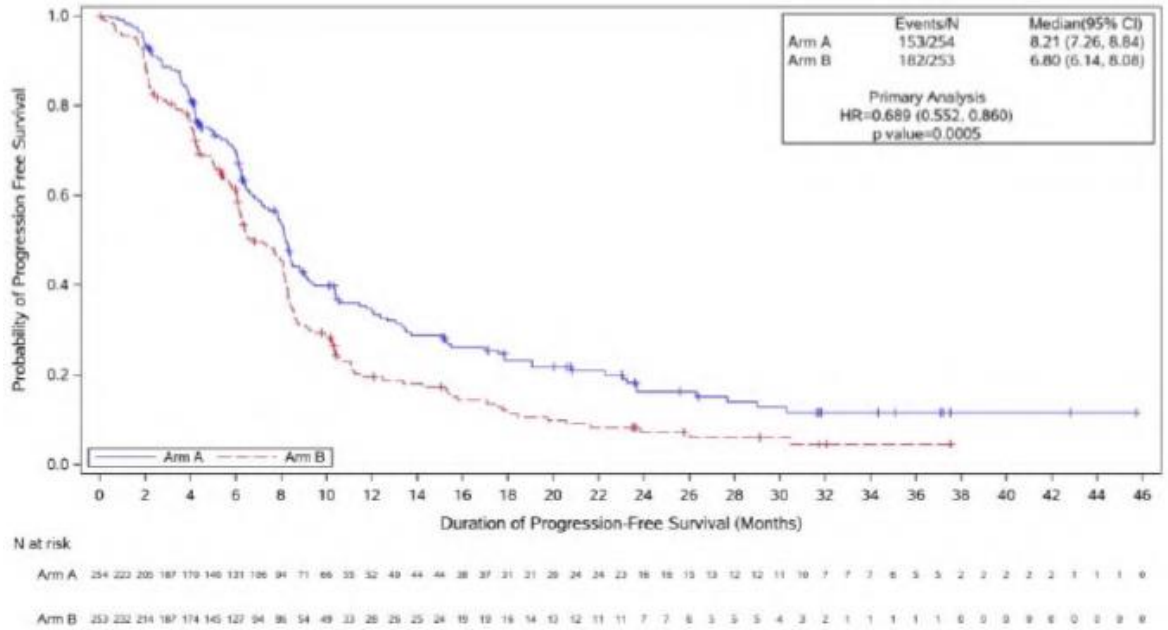
As of the primary analysis with a DCO of 07 Oct 2022, a statistically significant increase in PFS of 1.4 months was demonstrated in the add-on zolbetuximab arm over the CAPOX arm. The median PFS per IRC was 8.21 (95% CI: 7.46, 8.84) months in the add-on zolbetuximab arm and 6.80 (95% CI: 6.14, 8.08) months in the CAPOX arm (HR 0.687; 95% CI: 0.544, 0.866; one-sided p=0.0007). Results from the subgroup analyses for region (Asia vs non-Asia) (HR 0.583 vs 0.928), number of metastatic sites (0 to 2 vs ≥3) (HR 0.691 vs 0.682) and previous gastrectomy (yes vs no) (HR 0.726 vs 0.696) were consistent with those observed in the primary analysis.

In the final analysis (DCO of 12 Jan 2024), the PFS benefit of add-on zolbetuximab was maintained at 1.4 months.

GLOW: PFS as assessed by IRC

PFS	**Primary analysis DCO: 07 Oct 2022**		**Final analysis DCO: 12 Jan 2024**	
	Zolbetuximab + CAPOX (N=254)	**Placebo + CAPOX (N=253)**	**Zolbetuximab + CAPOX (N=254)**	**Placebo + CAPOX (N=253)**
PFS events, n (%)	137 (53.9)	172 (68.0)	153 (60.2)	182 (71.9)
Median, months (95% CI)	8.21 (7.46, 8.84)	6.80 (6.14, 8.08)	8.21 (7.26, 8.84)	6.80 (6.14, 8.08)
HR (95% CI) One-sided p-value	0.687 (0.544, 0.866) 0.0007		0.689 (0.552, 0.860) 0.0005	
Median follow-up time, months (95% CI)	12.62 (10.32, 15.21)	12.09 (10.25, 15.05)	20.57 (15.21, 23.62)	23.49 (10.38, 25.76)
12-month PFS (%) (95% CI)	34.86 (27.75, 42.05)	19.13 (13.50, 25.51)	34.05 (27.14, 41.06)	19.49 (13.96, 25.71)
24-month PFS (%) (95% CI)	14.49 (6.17, 26.19)	7.28 (2.99, 14.16)	16.19 (10.63, 22.80)	7.25 (3.69, 12.40)

GLOW: Kaplan-Meier plot of PFS assessed by IRC, final analysis



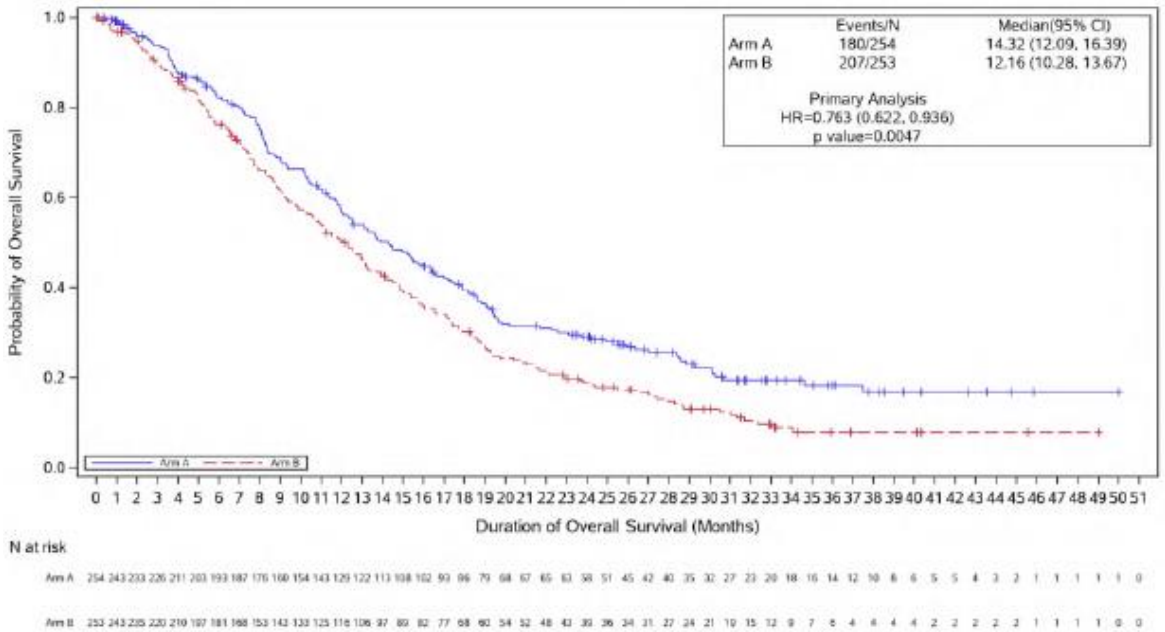
Arm A: Zolbetuximab + CAPOX; Arm B: Placebo + CAPOX

At the primary analysis, OS showed a statistically significant improvement of 2.2 months for the zolbetuximab combination compared to control. The median OS was 14.39 (95% CI: 12.29, 16.49) months in the zolbetuximab arm and 12.16 (95% CI: 10.28, 13.67) months in the CAPOX arm (HR 0.771; 95% CI: 0.615, 0.965; one-sided p=0.0118). The survival benefit was maintained at 2.2 months at the final analysis.

GLOW: OS results

OS	**Primary analysis DCO: 07 Oct 2022**		**Final analysis DCO: 12 Jan 2024**	
	Zolbetuximab + CAPOX (N=254)	**Placebo + CAPOX (N=253)**	**Zolbetuximab + CAPOX (N=254)**	**Placebo + CAPOX (N=253)**
No of events, n (%)	144 (56.7)	174 (68.8)	180 (70.9)	207 (81.8)
Median, months (95% CI)	14.39 (12.29, 16.49)	12.16 (10.28, 13.67)	14.32 (12.09, 16.39)	12.16 (10.28, 13.67)
HR (95% CI) One-sided p-value	0.771 (0.615, 0.965) 0.0118		0.763 (0.622, 0.936) 0.0047	
Median follow-up time, months (95% CI)	17.71 (16.33, 19.91)	18.43 (17.48, 20.80)	31.70 (28.19, 33.71)	32.95 (29.70, 35.91)
12-month OS (%) (95% CI)	57.54 (50.71, 63.77)	50.79 (44.12, 57.06)	56.68 (50.08, 62.75)	50.44 (43.89, 56.61)
24-month OS (%) (95% CI)	28.92 (21.75, 36.46)	17.38 (11.62, 24.12)	29.02 (23.21, 35.06)	18.81 (14.01, 24.16)

GLOW: Kaplan-Meier plot of OS, final analysis



Arm A: Zolbetuximab + CAPOX; Arm B: Placebo + CAPOX

Zolbetuximab doses of 800/600 mg/m^2 every 3 weeks were evaluated in the pivotal studies, with doses of 800/400 mg/m^2 every 2 weeks derived using modelling and simulation from the exposure-response model for efficacy and safety, as well as the tumour dynamic model. The population PK model predicted that the 800/400 mg/m^2 every 2 weeks regimen would have about 23% lower C_{max} at steady state and 9.7 to 21% higher C_{trough} across the treatment period as compared with the 800/600 mg/m^2 every 3 weeks regimen, with a comparable exposure metric. The difference in zolbetuximab exposure was not considered clinically relevant.

Taken together, 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-of-care chemotherapy in advanced gastric/GEJ adenocarcinoma.

D ASSESSMENT OF CLINICAL SAFETY

The safety profile of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy was based on the integrated safety data from the pivotal Phase III studies SPOTLIGHT and GLOW. At the primary analysis, a total of 533 patients received at least one dose of zolbetuximab, and the median duration of exposure to zolbetuximab was 171 days.

Overview of safety profile

TEAE, n (%)	SPOTLIGHT		GLOW		Integrated SPOTLIGHT/GLOW	
	Zolbetuximab + mFOLFOX6 (N=279)	Placebo + mFOLFOX6 (N=278)	Zolbetuximab + CAPOX (N=254)	Placebo + CAPOX (N=249)	Zolbetuximab + Chemotherapy (N=533)	Placebo + Chemotherapy (N=527)
Any TEAE	278 (99.6)	277 (99.6)	251 (98.8)	244 (98.0)	529 (99.2)	521 (98.9)
Zolbetuximab or placebo-related TEAE	255 (91.4)	216 (77.7)	231 (90.9)	168 (67.5)	486 (91.2)	384 (72.9)
SAE	125 (44.8)	121 (43.5)	120 (47.2)	124 (49.8)	245 (46.0)	245 (46.5)

Zolbetuximab or placebo-related SAE	47 (16.8)	28 (10.1)	50 (19.7)	39 (15.7)	97 (18.2)	67 (12.7)
TEAE leading to discontinuation of zolbetuximab or placebo	55 (19.7)	30 (10.8)	51 (20.1)	36 (14.5)	106 (19.9)	66 (12.5)
Zolbetuximab or placebo-related TEAE leading to discontinuation	38 (13.6)	6 (2.2)	18 (7.1)	11 (4.4)	56 (10.5)	17 (3.2)
Deaths due to TEAE	22 (7.9)	24 (8.6)	27 (10.6)	32 (12.9)	49 (9.2)	56 (10.6)

Data cut-off dates: SPOTLIGHT: 09 Sep 2022; GLOW: 07 Oct 2022
TEAE: Treatment-emergent adverse event
SAE: Serious adverse event

TEAEs were reported at high frequencies in both the add-on zolbetuximab and chemotherapy arms across both studies (99.2% vs 98.9%).

The most common treatment-related TEAEs included nausea (64.9% in the add-on zolbetuximab arm vs 36.1% in the chemotherapy arm), vomiting (59.1% vs 16.5%), decreased appetite (26.5% vs 19.9%) and neutropenia (14.3% vs 11.6%), while the most frequently reported treatment-related Grade ≥3 TEAEs included vomiting (11.8% vs 1.7%), nausea (9.9% vs 1.9%) and neutropenia (8.6% vs 6.6%). The increased toxicities were expected with add-on therapy and were consistent with the safety profile of the doublet chemotherapy backbone.

TEAEs leading to permanent discontinuation of zolbetuximab or placebo were reported in 19.9% of the patients in the add-on zolbetuximab arm vs 12.5% in the chemotherapy arm, with vomiting (3.8% vs 0.6%) and nausea (3.4% vs 0.4%) accounting for the majority of these TEAEs leading to permanent discontinuation of zolbetuximab or placebo.

Serious adverse events (SAEs) were reported in comparable frequencies in both the zolbetuximab (46.0%) and chemotherapy (46.5%) arms. Treatment-related SAEs were reported in 18.2% vs 12.7% respectively, which included vomiting (5.1% vs 1.1%), nausea (4.1% vs 1.1%), decreased appetite (1.7% vs 0.6%) and upper gastrointestinal (GI) haemorrhage (1.1% vs 0.2%). While such bleeding events could potentially be attributed to the underlying disease, the package insert was strengthened to reflect the observed imbalance in upper GI bleeds factually.

The frequencies of deaths due to TEAEs were comparable in both treatment arms (9.2% in the add-on zolbetuximab arm vs 10.6% in the chemotherapy arm). The causality relationship of related TEAEs resulting in death as assessed by the investigator were mostly confounded by the underlying malignancy and resulting immunocompromised state.

The most notable safety concerns with add-on zolbetuximab were nausea and vomiting, which were commonly observed during the first zolbetuximab infusion in the first cycle (48.7% to 67.4%) and with lower frequencies in subsequent cycles (approximately 10% to 30%). This might be attributed to the higher loading dose of zolbetuximab at the first infusion. The majority of these events were mild to moderate in severity and could be managed by adequate antiemetic premedication, dose interruptions and infusion rate adjustments. Notably, the incidences of Grade ≥3 nausea and vomiting events were reduced from between 8.7% to 16.1% in Cycle 1 to less than 2% in the later cycles which was reassuring. In view of the high incidences of nausea and vomiting, the package insert has been strengthened with detailed recommendations on ensuring an adequate coverage of antiemetics, especially in the first treatment cycle.

Other AEs of special interest (AESIs) included hypersensitivity reactions (add-on zolbetuximab: 35.8% vs chemotherapy: 32.3%) and infusion-related reactions (40.3% vs 11.0%). These AESIs were mostly mild to moderate in severity and could be managed by infusion rate reductions or interruptions.

One event of posterior reversible leukoencephalopathy syndrome (PRES) was reported in a patient who received zolbetuximab monotherapy in the Phase II study ILLUSTRO. As the causal relationship to zolbetuximab could not be entirely ruled out due to the temporal relationship and the limited safety experience of zolbetuximab, the package insert has included a warning for physicians to monitor patients for this rare AE, and to discontinue treatment promptly if PRES is suspected.

The updated integrated safety analysis at the final analysis, which was extended to include the Phase II studies, demonstrated consistent results with the primary analysis. Overall, the safety profile of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy is characterised by gastrointestinal AEs and hypersensitivity reactions, and no new safety signals were detected.

E ASSESSMENT OF BENEFIT-RISK PROFILE

In Singapore, gastric cancer is the fourth most common cause of cancer death in men and the fifth most common in women, with 300 to 500 lives lost to the disease every year. Gastric cancer is often asymptomatic in the early stages, and the disease is often diagnosed at an advanced stage with a poor survival prognosis.

Doublet fluoropyrimidine- and platinum-containing chemotherapy regimen is the current standard of care in the first-line setting for HER2-negative advanced gastric cancer, with a median overall survival duration of approximately 1 year. The addition of PD-1 inhibition to this backbone has demonstrated survival improvements, with greater benefit observed in patients with higher PD-L1 expression levels. However, there remains a clinical need for new treatment options, particularly for patients with low PD-L1 expression who may derive limited benefit from immunotherapy.

The two Phase III studies SPOTLIGHT and GLOW demonstrated consistent efficacy of zolbetuximab combined with doublet fluoropyrimidine- and platinum-containing chemotherapy in the overall population for the first-line treatment of HER2-negative and CLDN18.2-positive advanced gastric cancer, extending OS by 2.2 to 2.7 months and PFS by 1.4 to 2.1 months, compared to chemotherapy alone. Given that CLDN18.2 is highly expressed in approximately 40% of HER2-negative gastric cancer, zolbetuximab offers a new therapeutic option where effective treatments are limited.

Overall, the safety profile of add-on zolbetuximab to doublet chemotherapy showed increased toxicities as would be expected with combination therapy. The most notable safety concerns, nausea, vomiting and infusion-related reactions, were addressed with adequate warnings in the product labelling and considered manageable in the oncology practice.

Taking all evidence in totality, the benefit-risk assessment of zolbetuximab in the treatment of CLDN18.2-positive advanced gastric cancer was considered favourable.

F CONCLUSION

Based on the review of the quality, safety and efficacy data, the benefit-risk balance of Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive was deemed favourable and approval of the product registration was granted on 06 March 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

VYLOY™ POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 100 MG/VIAL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains an extractable amount of 100 mg zolbetuximab after reconstitution for a final concentration of 20 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white lyophilized powder for reconstitution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors are Claudin (CLDN) 18.2 positive (see section 5.1).

4.2 Posology and method of administration

Posology

Patient Selection

Select patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors are CLDN18.2 positive (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining) as determined by a validated test, for treatment with Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).

Prior to Administration

If a patient is experiencing nausea and/or vomiting prior to administration of Vyloy, the symptoms should be resolved to Grade ≤1 before administering the first infusion.

Recommended Pretreatment
Prior to each infusion of Vyloy, premedicate patients with a combination of antiemetics (e.g., NK-1 receptor blockers and/or 5-HT3 receptor blockers, as well as other drugs as indicated), for the prevention of nausea and vomiting (see section 4.4).

Pre-medication with a combination of antiemetics is important for the management of nausea and vomiting to prevent early treatment discontinuation of zolbetuximab (see section 4.4). Pre-medication with systemic corticosteroids per local treatment guidelines may also be considered particularly before the first infusion of zolbetuximab.

Recommended Dose

Table 1. Recommended Vyloy Dosage Based on Body Surface Area

Single Loading Dose	Maintenance Doses	Duration of Therapy
800 mg/m^2 intravenously, Cycle 1, Day 1[a] Administer Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[b]	600 mg/m^2 intravenously every 3 weeks or 400 mg/m^2 intravenously every 2 weeks[c] Administer Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[b]	Until disease progression or unacceptable toxicity.

a. The cycle duration of Vyloy is determined based on the respective chemotherapy backbone (see section 5.1).
b. Refer to the fluoropyrimidine- or platinum-containing chemotherapy prescribing information regarding the dosing information for chemotherapy.
c. See section 5.2 for information regarding the 800/400 mg/m^2 every 2 weeks regimen based on pharmacokinetic modelling and simulation.

Dose Modifications

No dose reduction for Vyloy is recommended. Adverse reactions for Vyloy are managed by infusion rate reduction, interruption, and/or discontinuation as presented in Table 2.

Table 2. Dose Modifications for Vyloy

Adverse Reaction	Severity[a]	Dose Modification
Hypersensitivity reactions (see section 4.4)	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 for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Infusion related reaction (see section 4.4)	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 for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Nausea (see section 4.4)	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. • For the next infusion, administer per the infusion rates in Table 3.
Vomiting (see section 4.4)	Grade 4	Permanently discontinue.
	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate 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.

Special Populations

Elderly
No dose adjustment is required in patients ≥65 years of age. Of the 533 patients in clinical studies of VYLOY in combination with mFOLFOX6 or CAPOX, 34% (n=179) were over 65 years, and 5% were over 75 years (n=28). No overall differences in safety or effectiveness were observed between patients aged 65 years or older and younger patients.

Pediatric population
The safety and efficacy of Vyloy in the pediatric population have not been established.

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Vyloy has only been evaluated in a limited number of patients with severe renal impairment.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Vyloy has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment.

Method of administration

Vyloy is for intravenous use. The recommended dose is administered by intravenous infusion over a minimum of 2 hours. Vyloy must not be administered as an intravenous push or bolus injection.

If Vyloy and fluoropyrimidine- and platinum-containing chemotherapy are administered on the same day, Vyloy must be administered first.

To help minimize potential adverse reactions, it is recommended that each infusion should be 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 (see Table 3).

If the infusion time exceeds the recommended storage time at room temperature (12 hours from end of preparation of infusion solution), the infusion bag must be discarded and a new infusion bag prepared to continue the infusion (see section 6.3 for recommended storage times).

Table 3. Infusion Rates Recommended for Each Vyloy Infusion

Vyloy Dose		**Infusion Rate**	
		First 30-60 minutes	**Remaining Infusion time**[b]
Single Loading Dose (Cycle 1, Day 1)[a]	800 mg/m^2	100 mg/m^2/hr	200-400 mg/m^2/hr
Maintenance Doses	600 mg/m^2 every 3 weeks	75 mg/m^2/hr	150-300 mg/m^2/hr
	Or	or	or
	400 mg/m^2 every 2 weeks[c]	50 mg/m^2/hr	100-200 mg/m^2/hr

a. The cycle duration of Vyloy 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.
c. See section 5.2 for information regarding the 800/400 mg/m^2 every 2 weeks regimen based on pharmacokinetic modelling and simulation.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Hypersensitivity reactions in patients treated with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy during clinical studies were characterized by anaphylactic reaction or drug hypersensitivity (see section 4.8).

Monitor patients during and after infusion with Vyloy (at least 2 hours, or longer if clinically indicated) for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (e.g., urticaria, repetitive cough, wheeze and throat tightness/change in voice).

If an anaphylactic reaction occurs, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy administered.

For any Grade 3 or 4 hypersensitivity reaction or hypersensitivity reaction with features of anaphylaxis, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy instituted based on the type of reaction.

For any Grade 2 hypersensitivity reaction, interrupt the Vyloy infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of a hypersensitivity reaction. The infusion rate may be gradually increased as tolerated (see section 4.2).

Infusion-related reaction

Infusion-related reaction (IRR) has occurred during clinical studies with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy (see section 4.8).

Monitor patients for signs and symptoms of infusion-related reaction 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.

For Grade 3 or 4 IRRs, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy instituted.

For Grade 2 IRRs, interrupt the Vyloy infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of an IRR. The infusion rate may be gradually increased as tolerated (see section 4.2).

Nausea and Vomiting

During clinical studies, nausea and vomiting were the most frequently observed gastrointestinal (GI) adverse reactions with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy treatment (see section 4.8).

Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment.

To prevent nausea and vomiting, pretreatment with a combination of antiemetics is recommended prior to each infusion of Vyloy (see section 4.2).

During and after infusion, patients should be monitored and managed using standard of care, including antiemetics or fluid replacement, as clinically indicated.

For Grade 4 vomiting, permanently discontinue treatment with Vyloy.

For Grade 2 or 3 nausea or vomiting, interrupt the Vyloy infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. For the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of nausea or vomiting. The infusion rate may be gradually increased as tolerated (see section 4.2).

Gastrointestinal Haemorrhage

Serious upper gastrointestinal (GI) haemorrhage has been observed in patients receiving Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy. In the clinical studies, serious upper GI haemorrhage occurred more frequently in patients receiving zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy [1.0% (6/631)) in comparison with patients receiving placebo in combination with fluoropyrimidine and platinum-containing chemotherapy [0.2% (1/611)]. Monitor patients for signs and symptoms of upper GI haemorrhage during treatment. Promptly evaluate and treat any suspected upper GI haemorrhage.

Posterior Reversible Encephalopathy Syndrome (PRES)

One event of PRES has been reported in a patient. This is a rare reversible, neurological disorder that can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of zolbetuximab treatment in patients who develop PRES is recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Zolbetuximab is not a cytokine modulator and there are no known effects of its mechanism of action on cytochrome P450 or drug transporters; therefore, no *in vitro* or *in vivo* drug-drug interaction or transporter studies have been conducted.

Based on a phase 2 study, coadministration of zolbetuximab with mFOLFOX6 did not show a clinically meaningful change in drug exposure of zolbetuximab, oxaliplatin, or 5-fluorouracil (5-FU). Therefore, no dose adjustment is required for zolbetuximab and mFOLFOX6 when used in combination.

This finding is also expected to be applicable to CAPOX, which contains oxaliplatin and capecitabine (a prodrug of 5-FU), therefore no dose adjustment is required for zolbetuximab and CAPOX when used in combination.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of zolbetuximab in pregnant women. In an embryo-fetal development toxicity study, where zolbetuximab was administered to pregnant mice during the period of organogenesis at doses up to 300 mg/kg (up to approximately 35 times the recommended human dose of 600 mg/m^2, based on AUC), zolbetuximab crossed the placental barrier and did not result in any external or visceral fetal abnormalities (malformations or variations). Vyloy should only be given to a pregnant woman if the benefit outweighs the potential risk.

Breast-feeding

There are no data on the presence of zolbetuximab in human milk, the effects on the breastfed child, or the effects on milk production. It is known that antibodies (including IgG1) are excreted in human milk and because of the potential for serious adverse effects in a breastfed child, breastfeeding is not recommended during treatment with Vyloy.

Fertility
Fertility studies have not been performed with zolbetuximab.

4.7 Effects on ability to drive and use machines

No studies with zolbetuximab and the effects on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions with zolbetuximab were nausea (77.2%), vomiting (66.9%), decreased appetite (42%), neutropenia (30.7%), neutrophil count decreased (28.4%), weight decreased (21.9%), pyrexia (17.4%), hypoalbuminaemia (17.1%), oedema peripheral (13.9%), hypertension (9%), dyspepsia (7.8%), chills (5.2%), salivary hypersecretion (3.8%), infusion related reaction (3.2%) and drug hypersensitivity (1.6%).

Serious adverse reactions occurred in 45% of patients treated with zolbetuximab. The most common serious adverse reactions were vomiting (6.8%), nausea (4.9%), and decreased appetite (1.9%).

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 60.9% of patients; the most common adverse reactions leading to dose interruption were vomiting (26.6%), nausea (25.5%), neutropenia (9.8%), neutrophil count decreased (5.9%), hypertension (3.2%), chills (2.2%), infusion related reaction (1.6%), decreased appetite (1.6%), and dyspepsia (1.1%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on two phase 2 studies and two phase 3 studies in 631 patients who received at least one dose of zolbetuximab 800 mg/m^2 as a loading dose followed by 600 mg/m^2 maintenance doses every 3 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy. Patients were exposed to zolbetuximab for a median duration of 174 days (range: 1 to 1791 days).

Adverse reactions observed during clinical studies are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse Reactions

MedDRA System organ class	Adverse reaction	Frequency category
Blood and lymphatic system disorders	Neutropenia	Very common
	Neutrophil count decreased	
Immune system disorders	Drug hypersensitivity	Common
	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypoalbuminaemia	Very common
	Decreased appetite	
Vascular disorders	Hypertension	Common
Gastrointestinal disorders	Vomiting	Very common
	Nausea	
	Dyspepsia	Common
	Salivary hypersecretion	
General disorders and administration site conditions	Pyrexia	Very common
	Oedema peripheral	

MedDRA System organ class	Adverse reaction	Frequency category
	Chills	Common
Investigations	Weight decreased	Very common
Injury, poisoning and procedural complications	Infusion related reaction	Common

Selected Adverse Reactions

Hypersensitivity reactions

In the integrated safety analysis, all grade anaphylactic reaction or drug hypersensitivity occurred less frequently in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631), 1.6% (10/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.8% (5/611), 1.6% (10/611)]. Severe (Grade 3) anaphylactic reaction or drug hypersensitivity occurred at a similar frequency in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631), 0.2% (1/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.3% (2/611), 0.2% (1/611)]. The median time to onset of anaphylactic reaction or drug hypersensitivity with zolbetuximab and/or with fluoropyrimidine and platinum containing chemotherapy was 22 days or 113 days, respectively.

Three patients (0.5%) permanently discontinued zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy due to anaphylactic reaction. Dose interruption of zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy was experienced due to drug hypersensitivity in six patients (1.0%). The infusion rate was reduced for zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in one patient (0.2%) due to drug hypersensitivity.

Infusion related reaction

In the integrated safety analysis, all grade IRR occurred in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 3.2% (20/631) compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 1.1% (7/611). Severe (Grade 3) IRR occurred more frequently in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0% (0/611)]. The median time to onset of infusion-related reaction with zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy was 22 days.

An IRR led to permanent discontinuation of zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in 4 (0.6%) patients and dose interruption in 10 (1.6%) patients. The infusion rate was reduced for zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in 2 patients (0.3%) due to an IRR.

Nausea and vomiting

In the integrated safety analysis, all grade nausea or vomiting occurred more frequently in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy arm [77.2% (487/631), 66.9% (422/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [58.9% (360/611), 36.8% (225/611)]. Severe (Grade 3) nausea or vomiting in the zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy and placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arms occurred at the following frequencies: nausea (11.6%; 73/631, 4.7%; 29/611) or vomiting (13.6%; 86/631, 4.7%; 29/611). 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.

Nausea led to permanent discontinuation of zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in 27 (4.3%) patients and dose interruption in 179 (28.4%) patients. Vomiting led to permanent discontinuation of zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in 34 (5.4%) patients and dose interruption in 185 (29.3%) patients. The infusion rate was reduced for zolbetuximab and/or fluoropyrimidine and platinum-containing chemotherapy in 61 patients (9.7%) due to nausea and in 49 patients (7.8%) due to vomiting.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

In case of overdose, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX31.

Mechanism of action

Zolbetuximab is a genetically engineered, highly purified 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. Antitumor results observed in murine tumor models were variable, with significant antitumor effects in some models and minimal or no antitumor effects in other models. Zolbetuximab in combination with chemotherapeutics significantly improved tumor inhibition, compared with zolbetuximab or chemotherapeutics alone, in immunocompetent mice, but tumor growth inhibition was not different from chemotherapeutics alone in immunocompromised mice.

Concentration-QTc Interval

At the recommended dosage, zolbetuximab had no clinically meaningful effect on QTc prolongation.

Clinical efficacy and safety

Gastric or GEJ Adenocarcinoma
Combined SPOTLIGHT (8951-CL-0301) and GLOW (8951-CL-0302)
The safety and efficacy of Vyloy in combination with chemotherapy was evaluated in two phase 3, double-blind, randomised, multicenter studies that enrolled 1072 patients whose tumors were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. CLDN18.2 positivity (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GEJ tumor tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay performed in a central laboratory.

In each phase 3 study, patients were randomised 1:1 to receive either zolbetuximab in combination with chemotherapy (n=537) or placebo in combination with chemotherapy (n=535). Zolbetuximab was

administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by a maintenance dose of 600 mg/m^2 every 3 weeks in combination with mFOLFOX6 (SPOTLIGHT) or CAPOX (GLOW).

Patients were excluded from the studies if they had a complete or partial gastric outlet syndrome, positive test for human immunodeficiency virus (HIV) infection or known active hepatitis B or C infection, significant cardiovascular disease (e.g., congestive heart failure per New York Heart Association Class III or IV, history of significant ventricular arrhythmias, QTc interval >450 msec for males; >470 msec for females) or history of central nervous system metastases.

Patients in the SPOTLIGHT study received up to 12 treatments (4 cycles) of mFOLFOX6 [oxaliplatin 85 mg/m^2, folinic acid (leucovorin or local equivalent) 400 mg/m^2, fluorouracil 400 mg/m^2 given as a bolus and fluorouracil 2400 mg/m^2 given as a continuous infusion] administered on Days 1, 15 and 29 of a 42-day cycle. After 12 treatments, patients were allowed to continue treatment with zolbetuximab, 5-fluorouracil and folinic acid (leucovorin or local equivalent) at the discretion of the investigator, until progression of disease or unacceptable toxicity.

Patients in the GLOW study received up to 8 treatments (8 cycles) of CAPOX administered on Day 1 (oxaliplatin 130 mg/m^2) and on Days 1 to 14 (capecitabine 1000 mg/m^2) of a 21-day cycle. After 8 treatments of oxaliplatin, patients were allowed to continue treatment of zolbetuximab and capecitabine at the discretion of the investigator, until progression of disease or unacceptable toxicity.

The primary efficacy outcome was PFS as assessed per RECIST v1.1 by IRC. The key secondary efficacy outcome was OS. Other secondary efficacy outcomes were ORR and DOR as assessed per RECIST v1.1 by IRC.

Table 5 summarizes the primary analysis (final PFS, interim OS) baseline characteristics for SPOTLIGHT, GLOW, and SPOTLIGHT/GLOW combined.

Table 5. Baseline characteristics in SPOTLIGHT, GLOW and SPOTLIGHT/GLOW combined (primary analysis)

Category	SPOTLIGHT		GLOW		SPOTLIGHT/GLOW Combined	
	Vyloy with mFOLFOX 6 n=283	**Placebo with mFOLFOX 6 n=282**	**Vyloy with CAPOX n=254**	**Placebo with CAPOX n=253**	**Vyloy with mFOLFOX 6/ CAPOX n=537**	**Placebo with mFOLFOX 6/ CAPOX n=535**
Age (years)						
Median age (range)	62 (27 to 83)	60 (20 to 86)	61 (22 to 82)	59 (21 to 83)	61 (22 to 83)	60 (20 to 86)
≥18 to ≤64 (%)	60	62	66	68	63	65
≥65 (%)	40	38	34	32	37	35
Race (%)						
White	54	53	37	36	46	45
Asian	37	38	63	64	50	51
American Indian or Alaskan	3	3	0	0	2	2
Black or African American	2	1	0	0	1	0
Other	4	5	0	0	2	2
Gender (%)						
Male	62	62	63	62	62	62
Female	38	38	37	38	38	38
ECOG performance status						
0 (%)	45	41	43	43	44	42
1 (%)	55	59	57	57	56	58
Missing data (n)	4	4	1	3	5	7
Medical condition						
Gastric Adenocarcinoma (%)	77	75	86	82	82	78
Gastro-Esophageal Junction Adenocarcinoma (%)	23	26	14	17	18	22
Tumor metastatic						
Yes (%)	85	84	87	88	86	86
No (%)	16	16	13	12	14	14
Mean body surface area (m^2), (range)	1.7 (1.2 to 2.4)	1.7 (1.1 to 2.5)	1.7 (1.2 to 2.3)	1.7 (1.1 to 2.3)	1.7 (1.2 to 2.4)	1.7 (1.1 to 2.5)
Median time from diagnosis (days), (range)	56 (2 to 3010)	56 (7 to 5366)	44 (12 to 2396)	44 (2 to 6010)	49 (2 to 3010)	50 (2 to 6010)
Tumor location						
Distal (%)	39	42	39	38	39	40
Proximal (%)	37	30	35	37	36	34
Unknown (%)	24	28	26	25	25	26
Missing (n)	3	1	0	0	3	1
Tumor types						
Diffuse (%)	29	42	34	40	32	41
Intestinal (%)	25	24	14	16	20	20
Other (%)	18	15	13	11	16	13
Mixed (%)	11	5	8	8	10	6
Unknown (%)	17	14	30	25	23	20
Missing (n)	1	4	1	0	2	4

The primary efficacy outcome was progression-free survival (PFS) as assessed per RECIST v1.1 by an independent review committee (IRC). The key secondary efficacy outcome was overall survival (OS). Other secondary efficacy outcomes were objective response rate (ORR) and duration of response (DOR) as assessed per RECIST v1.1 by IRC.

In the primary analysis (final PFS and interim OS), the SPOTLIGHT study demonstrated a statistically significant benefit in PFS (as assessed by IRC) and OS for patients who received zolbetuximab in combination with mFOLFOX6 compared with patients who received placebo in combination with mFOLFOX6 treatment. The PFS HR was 0.751 (95% CI: 0.598, 0.942; 1-sided P = 0.0066) and the OS HR was 0.750 (95% CI: 0.601, 0.936; 1-sided P = 0.0053).

The updated PFS and final OS analysis for SPOTLIGHT are presented in table 6 and Figures 1-2 show the Kaplan- Meier curves.

In the primary analysis (final PFS and interim OS), the GLOW study demonstrated a statistically significant benefit in PFS (as assessed by IRC) and OS for patients who received zolbetuximab in combination with CAPOX compared with patients who received placebo in combination with CAPOX treatment. The PFS HR was 0.687 (95% CI: 0.544, 0.866; 1-sided P = 0.0007) and the OS HR was 0.771 (95% CI: 0.615, 0.965; 1-sided P = 0.0118).

The updated PFS and final OS analysis for GLOW are presented in table 6 and Figures 3-4 show the Kaplan- Meier curves.

Table 6. Efficacy results in SPOTLIGHT and GLOW

	SPOTLIGHT[a]		**GLOW[b]**	
Endpoint	**Zolbetuximab with mFOLFOX6 n=283**	**Placebo with mFOLFOX6 n=282**	**Zolbetuximab with CAPOX n=254**	**Placebo with CAPOX n=253**
Progression-free survival				
Number (%) of patients with events	159 (56.2)	187 (66.3)	153 (60.2)	182 (71.9)
Median in months (95% CI)[c]	11.0 (9.7, 12.5)	8.9 (8.2, 10.4)	8.2 (7.3, 8.8)	6.8 (6.1, 8.1)
Hazard ratio (95% CI)[d,e]	0.734 (0.591, 0.910)		0.689 (0.552, 0.860)	
Overall survival				
Number (%) of patients with events	197 (69.6)	217 (77.0)	180 (70.9)	207 (81.8)
Median in months (95% CI)[c]	18.2 (16.1, 20.6)	15.6 (13.7, 16.9)	14.3 (12.1, 16.4)	12.2 (10.3, 13.7)
Hazard ratio (95% CI)[d,e]	0.784 (0.644, 0.954)		0.763 (0.622, 0.936)	
Objective response rate (ORR), Duration of response (DOR)				
ORR (%) (95% CI)[f]	48.1 (42.1, 54.1)	47.5 (41.6, 53.5)	42.5 (36.4, 48.9)	39.1 (33.1, 45.4)
DOR Median in months (95% CI)[f]	9.0 (7.5, 10.4)	8.1 (6.5, 11.4)	6.3 (5.4, 8.3)	6.1 (4.4, 6.3)

a. SPOTLIGHT data cut-off: 08-Sep-2023, median follow-up time of zolbetuximab in combination with mFOLFOX6 arm was 18.0 months.
b. GLOW data cut-off: 12-Jan-2024, median follow-up time of zolbetuximab in combination with CAPOX arm 20.6 months.
c. Based on Kaplan-Meier estimate.
d. Stratification factors were region, number of metastatic sites, prior gastrectomy from interactive response technology and study ID (SPOTLIGHT/GLOW).

e. Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy as the explanatory variables and study ID (SPOTLIGHT/GLOW).
f. Based on IRC assessment and unconfirmed responses.

A combined efficacy analysis of SPOTLIGHT and GLOW of the final OS and updated PFS resulted in a median PFS (as assessed by IRC) of 9.2 months (95% CI: 8.4, 10.4) for zolbetuximab in combination with mFOLFOX6/CAPOX versus 8.2 months (95% CI: 7.6, 8.4) for placebo with mFOLFOX6/CAPOX [HR 0.712, 95% CI: 0.610, 0.831] and a median OS for zolbetuximab in combination with mFOLFOX6/CAPOX of 16.4 months (95% CI: 15.0, 17.9) versus 13.7 months (95% CI: 12.3, 15.3) for placebo with mFOLFOX6/CAPOX [HR 0.774, 95% CI: 0.672, 0.892].

Figure 1. Kaplan Meier plot of progression-free survival, SPOTLIGHT

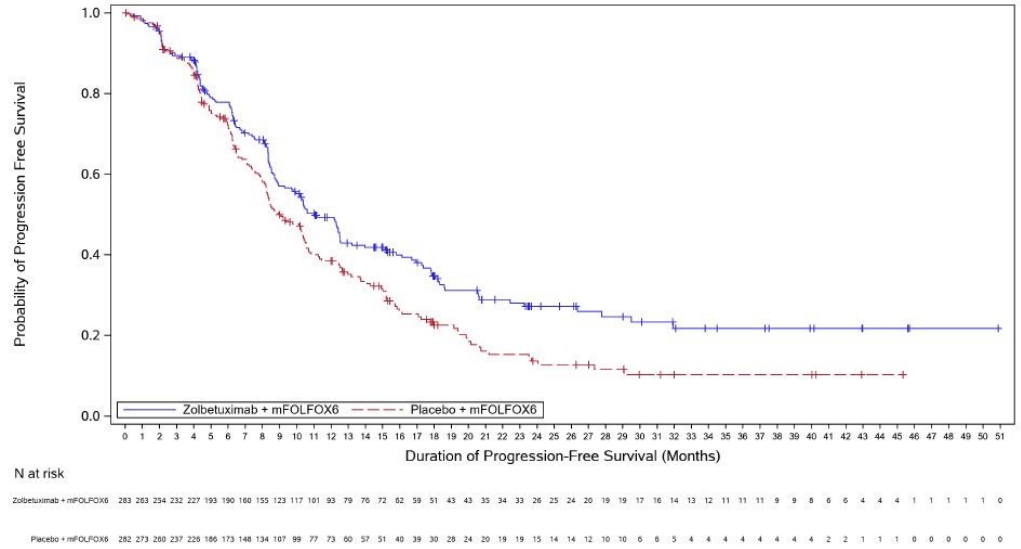


Figure 2. Kaplan Meier plot of overall survival, SPOTLIGHT

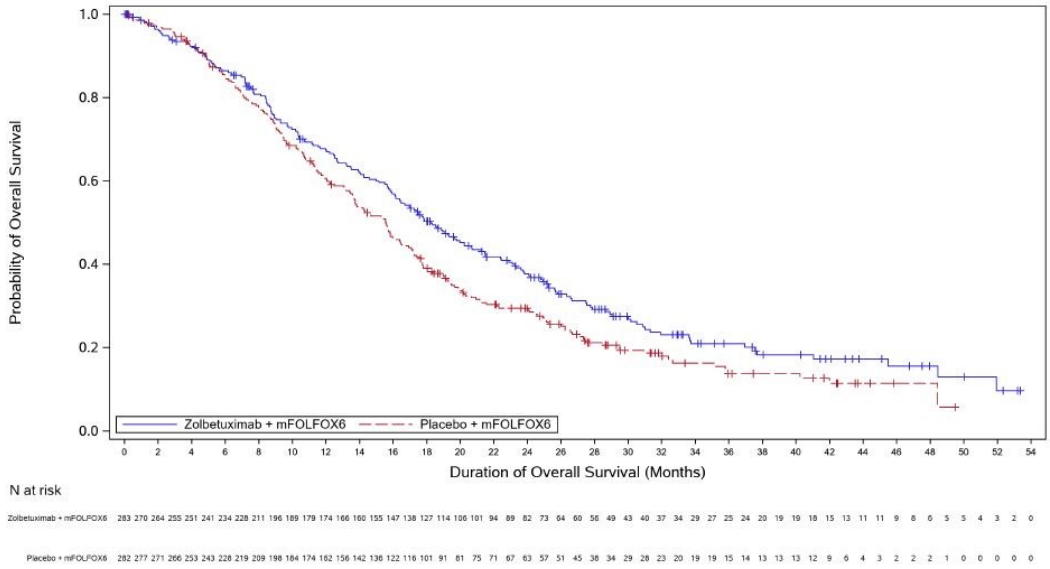


Figure 3. Kaplan Meier plot of progression-free survival, GLOW

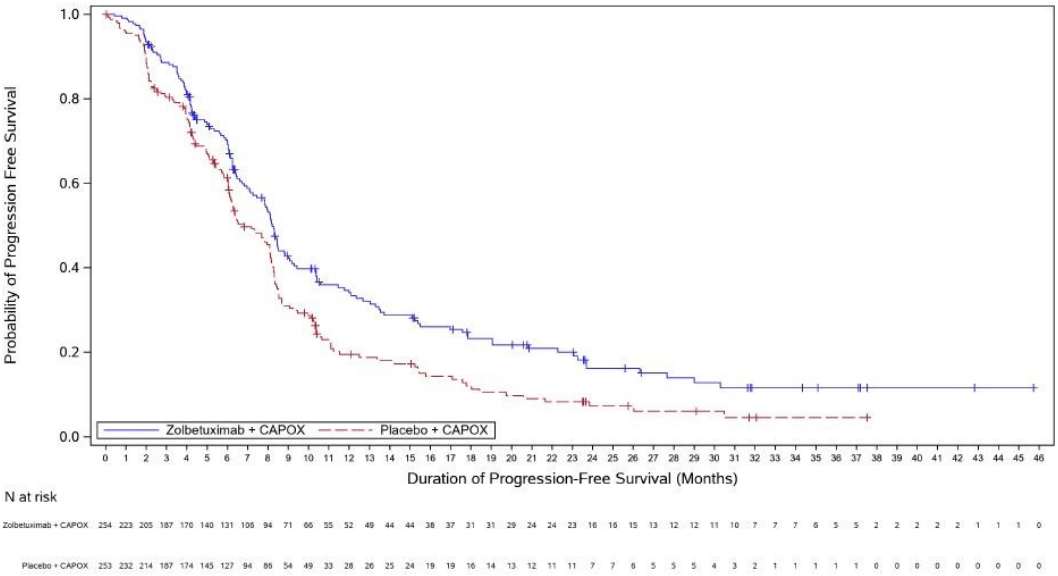
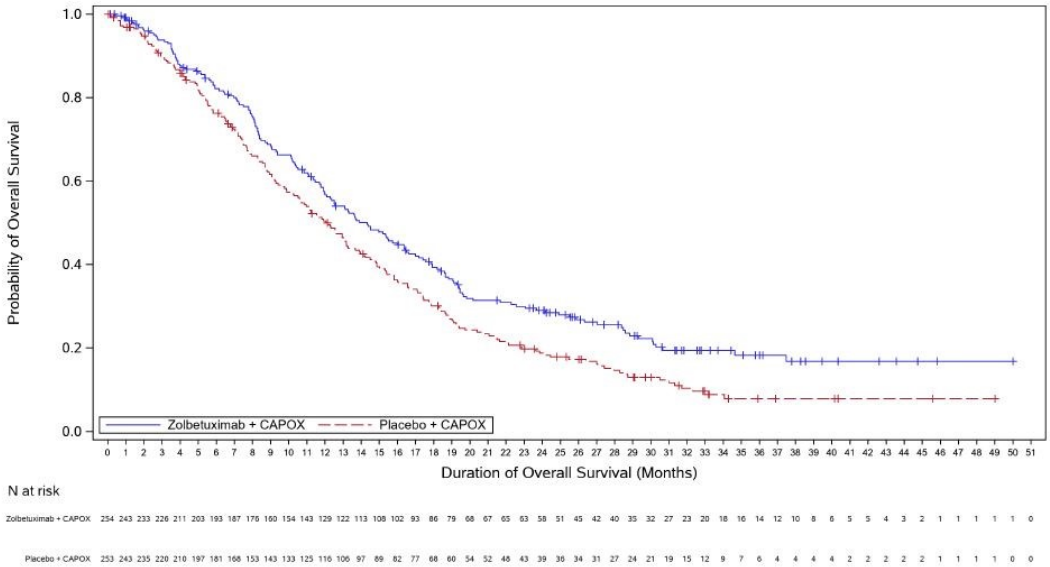


Figure 4. Kaplan Meier plot of overall survival, GLOW



5.2 Pharmacokinetic properties

Following intravenous administration, zolbetuximab exhibited dose-proportional pharmacokinetics at doses ranging from 33 mg/m^2 to 1000 mg/m^2. When administered at 800/600 mg/m^2 every 3 weeks, steady state was achieved by 18 weeks with a mean (SD) C_{max} and AUC_{tau} at 425 (91) µg/mL and 3359 (1254) day•µg/mL, respectively.

Distribution
The estimated mean steady state volume of distribution of zolbetuximab was 16.4 L.

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

Elimination
The estimated mean clearance (CL) and $t_{1/2}$ of zolbetuximab was 0.0150 L/h and 43.6 d, respectively.

Special Populations

Elderly
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.

Race and gender
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% White, 42.2% Asian, 4.2% Missing, 2.7% Others, and 0.8% Black].

Renal impairment
Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild (CrCL ≥60 to <90 mL/min; n=298) to moderate (CrCL ≥30 to <60 mL/min; n=109) renal impairment based on creatinine clearance (CrCL) estimated by the Cockcroft-Gault (C-G) formula. Zolbetuximab has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min; n=1).

Hepatic impairment
Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild hepatic impairment as measured by total bilirubin (TB) and aspartate aminotransferase (AST) (TB ≤ upper limit of normal (ULN) and AST > ULN, or TB > 1 to 1.5 x ULN and any AST; n=108). Zolbetuximab has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST; n=4) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 x ULN and any AST).

Immunogenicity
In an approximately 30-month treatment period of 2 clinical studies of zolbetuximab 800/600 mg/m^2 every 3 weeks in combination with mFOLFOX6/CAPOX in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors are CLDN18.2 positive, the incidence of treatment emergent anti-zolbetuximab antibody formation was 4.4% [21 of 479 total zolbetuximab-treated patients who were tested for anti-drug antibodies (ADAs)]. Because of the low occurrence of immunogenicity, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown.

Pharmacokinetic/pharmacodynamic relationship
Zolbetuximab doses of 800/600 mg/m^2 every 3 weeks were evaluated in clinical studies, with doses of 800/400 mg/m^2 every 2 weeks derived using modelling and simulation from the exposure-response model for efficacy and safety, as well as the tumour dynamic model.

The population PK model predicted that the 800/400 mg/m^2 every 2 weeks dosing regimen will have about 23% lower C_{max} at steady state and 9.7-21% higher C_{trough} across the treatment period compared to the 800/600 mg/m^2 every 3 weeks regimen. However, the exposure-response analysis based on the population PK model showed no anticipated clinically significant differences in efficacy or safety between the two dosing regimens.

5.3 Preclinical safety data

Genotoxicity
No data available.

Carcinogenicity
No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Table 7. List of excipients

Component	Extractable Amount per Vial
Arginine	116.2 mg
Phosphoric Acid	q.s. to pH 6.0
Sucrose	256.48 mg
Polysorbate 80	1.05 mg

6.2 Incompatibilities

Do not co-administer other drugs through the same infusion line.

6.3 Shelf life

Unopened vial
The expiry date can be found on the packaging.

Reconstituted vial
Reconstituted vials may be stored at room temperature (not more than 30ºC) for up to 6 hours. Do not freeze. Do not expose to direct sunlight. Discard unused vials with reconstituted solution beyond the recommended storage time.

Prepared infusion bag
The prepared infusion bag should be administered immediately. If not administered immediately, the prepared infusion bag should be stored:

- under refrigeration at 2°C to 8°C for no longer than 24 hours including infusion time from the end of the preparation of the infusion bag. Do not freeze.
- at room temperature (not more than 30ºC) for no longer than 12 hours including infusion time from when the prepared infusion bag is removed from the refrigerator. Do not expose to direct sunlight.

Discard unused prepared infusion bags beyond the recommended storage time.

6.4 Special precautions for storage

Package type	Recommended storage conditions
Lyophilized, unopened, clear 20 mL glass vial	Store at 2ºC to 8ºC

6.5 Nature and contents of container

Clear Type I 20 mL glass vial with European blow-back feature
Gray bromobutyl rubber stopper with ethylene tetrafluoroethylene film
20 mm aluminum seal with a green cap
Pack size: one carton containing 1 vial

6.6 Special precautions for use, handling and disposal

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

3. Calculate the recommended dose based on the patient's body surface area to determine the number of vials needed.
4. Reconstitute the vial by slowly adding 5.0 mL of Sterile Water For Injection (SWFI). If possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilized powder. The reconstituted solution contains 20 mg/mL of zolbetuximab.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle. Visually inspect the solution until the bubbles are gone. Do not shake the vial.
6. Visually inspect the solution for particulate matter and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless to slight yellow and free of visible particles. Discard any vial with visible particles or discoloration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, refer to section 6.3 for storage of reconstituted vials.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute zolbetuximab with 0.9% Sodium Chloride Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 2 mg/mL zolbetuximab.

The diluted dosing solution of zolbetuximab is compatible with intravenous infusion bags composed of polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with either plasticizer [Di-(2-ethylhexyl) phthalate (DEHP) or Trioctyl trimellitate (TOTM)], ethylene propylene copolymer, ethylene-vinyl acetate (EVA) copolymer, PP and styrene-ethylene-butylene-styrene copolymer, or glass (bottle for administration use), and infusion tubing composed of PE, PVC with either plasticizer [DEHP, TOTM or Di-(2-ethylhexyl) terephthalate], polybutadiene (PB), or elastomer modified PP with in-line filter membranes (pore size 0.2 μm) composed of polyethersulfone (PES) or polysulfone.

10. Mix diluted solution by gentle inversion. Do not shake the bag.
11. Visually inspect the infusion bag for any particulate matter prior to use. The diluted solution should be free of visible particles. Do not use the infusion bag if particulate matter is observed.
12. Discard any unused portion left in the single-dose vials.

Administration

13. Do not co-administer other drugs through the same infusion line.
14. Immediately administer the infusion over a minimum of 2 hours through an intravenous line. Do not administer as an IV push or bolus.

No incompatibilities have been observed with closed system transfer device composed of PP, PE, stainless steel, silicone (rubber/oil/resin), polyisoprene, PVC or with plasticizer [TOTM], acrylonitrile-butadiene-styrene (ABS) copolymer, methyl methacrylate-ABS copolymer, thermoplastic elastomer, polytetrafluoroethylene, polycarbonate, PES, acrylic copolymer, polybutylene terephthalate, PB, or EVA copolymer.

No incompatibilities have been observed with central port composed of silicone rubber, titanium alloy or PVC with plasticizer [TOTM]. In-line filters (pore size of 0.2 μm with materials listed above) are recommended to be used during administration.

15. If not administered immediately, refer to section 6.3 for storage of the prepared infusion bag.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

Astellas Pharma Singapore Pte. Ltd.
6 Temasek Boulevard
#26-03/05 Suntec Tower Four
Singapore 038986
For any enquiry, please write to pv@sg.astellas.com.

8. DATE OF REVISION OF PACKAGE INSERT

FEB2025 (CCDSv3)