29 July 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vyloy (Chimeric monoclonal antibody against claudin-18 splice variant 2)
Treatment of gastric cancer
EU/3/10/803

Sponsor: Astellas Pharma Europe B.V.

Note

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

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1. Product and administrative information

Product	
Designated active substance(s)	Chimeric monoclonal antibody against claudin-18 splice variant 2
Other name(s)	Vyloy, Chimeric monoclonal antibody against claudin-18 splice variant 2
International Non-Proprietary Name	Zolbetuximab
Tradename	Vyloy
Orphan condition	Treatment of gastric cancer
Sponsor's details:	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden Zuid-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	GANYMED Pharmaceuticals AG
COMP opinion	09 September 2010
EC decision	26 November 2010
EC registration number	EU/3/10/803
Post-designation procedural history	
Transfer of sponsorship	Transfer from Ganymed Pharmaceuticals AG GmbH to Astellas Pharma Europe B.V. – EC decision of 26 March 2018
Sponsor's name change	Name change from GANYMED Pharmaceuticals AG to Ganymed Pharmaceuticals AG GmbH – EC letter of 22 May 2017
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Jan Mueller-Berghaus / Carolina Prieto Fernandez
Applicant	Astellas Pharma Europe B.V.
Application submission	21 June 2023
Procedure start	13 July 2023
Procedure number	EMA/H/C/005868/0000
Invented name	Vyloy

Proposed therapeutic indication	Zolbetuximab is indicated in adults for the treatment of patients with HER2-negative, metastatic or locally advanced unresectable gastric or gastroesophageal junction adenocarcinoma whose tumors express CLDN18.2 (moderate to strong staining in ≥ 75% of tumor cells) as determined by a validated immunohistochemistry (IHC) assay, in combination with platinum-and fluoropyrimidine-based chemotherapy. Further information can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Vyloy
CHMP opinion	25 July 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Brigitte Schwarzer-Daum / Frauke Naumann-Winter
Sponsor's report submission	01 February 2024
COMP discussion and adoption of list of questions	18-20 June 2024
Oral explanation	17 July 2024
COMP opinion (adoption via written procedure)	29 July 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2010 designation was based on the following grounds:

- gastric cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made;
- the condition is chronically debilitating and life threatening due to poor overall survival;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that chimeric monoclonal antibody against claudin-18 splice variant 2 may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on a novel (alternative) mechanism of action, supported by the presented preclinical data.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Gastric cancer (GC) includes adenocarcinoma of the gastroesophageal junction (GEJ) and stomach and there are no changes to the definition of the condition since the initial orphan designation.

Histologically GCs are mostly adenocarcinomas and may be described as cardia and non-cardia based on their anatomic site. Cancers of the gastric cardia arise in the region adjoining the oesophageal-gastric junction and thus share epidemiological characteristics with oesophageal adenocarcinoma. Non-cardia cancer, also known as distal stomach cancer, is more common. (Rawla et al, Prz Gastroenterol. 2019; 14(1): 26–38.)

On the basis of the Lauren classification, GC is histologically divided into the 3 subtypes: well differentiated (non-cardia/intestinal), poorly differentiated (cardia/diffuse) and mixed disease. The World Health Organization (WHO) classification system expands on this with 4 subtypes: papillary, tubular, signet ring and mucinous (Sexton RE et al, 2020).

Risk factors for the condition include H.Pylori infection, age, high salt intake, and diets low in fruit and vegetables. It is diagnosed histologically after endoscopic biopsy and staged using CT, endoscopic ultrasound, PET, and laparoscopy (Smyth et al, Lancet 2020 Aug 29;396(10251):635-648.)

The COMP continues to accept GC as a suitable orphan condition and includes the GEJ adenocarcinoma location in the designations.

The approved therapeutic 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 (see section 5.1)." falls within the scope of the designated orphan condition "Treatment of gastric cancer".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The chronically debilitating and life-threatening nature of the condition has not changed since the initial orphan designation.

In Europe, the 5-year survival rate of gastric cancer (all stages combined) is 26% but is as low as 19% in the UK and as high as 42% among women in Iceland [Rawla & Barsouk, 2019] and most patients with gastric cancer are diagnosed with advanced disease or develop disease recurrence after surgery with curative intent [Wagner et al, 2017].

The sponsor has submitted a description of the life-threatening aspects of the disease but does not discuss if the condition is chronically debilitating.

In the context of other designations, the COMP has considered that the condition is life threatening and chronically debilitating due to dysphagia, weight loss and gastric bleeding.

Number of people affected or at risk

At the time of the initial orphan designation in 2010 the prevalence was estimated to 3 in 10,000. For the maintenance procedure the sponsor bases the prevalence estimate on GLOBOCAN data.

In Europe, the highest incidence and mortality rates of gastric cancer are in Central-Eastern Europe (17.4 and 13.1 per 100 000 population in males and 7.1 and 5.1 per 100 000 population in females, respectively). The lowest rates are in Northern Europe (6.2 and 3.9 per 100 000 population in males and 3.1 and 2.0 per 100 000 population in females, respectively) [Morgan et al, 2022]. Although the overall incidence of gastric cancer has declined over the past 50 years in Western countries, there is an increase in incidence in adults under 50 years of age that impacts both high-risk and low-risk countries [Sung et al, 2021].

Based on GLOBOCAN data, it is estimated that, in the year 2020, gastric cancer was the fifth most common cancer diagnosed worldwide with 1.1 million newly diagnosed cases, and the fourth leading cause of cancer death with 769,000 deaths registered worldwide [Sung et al, 2021].

In the EU, between 1998 and 2016, and based on data from 18 member states including the 5 largest countries (France, Germany, Italy, Poland, Spain), the incidence and mortality rates of gastric cancer decreased by about 3% and 4% per year on average, respectively. According to the sponsor, there are no data available on trends in the EU after 2016 [Ferlay et al, 2020].

Since the estimated annual percent change in the incidence rate can be assumed to broadly offset the estimated annual change in the mortality rate for gastric cancer in the EU after 2020, the projected prevalence of gastric cancer in 2024, expressed as the number of cases per 10,000 individuals, would be expected to be similar to that in 2020. The sponsor estimates the prevalence of gastric cancer in 2024 in the EU to be about 2.7 per 10,000 individuals.

It is not clear from the submission how the final proposed prevalence estimate was derived and it would also be useful to have more EU sources of data in order to confirm and verify the proposed estimate.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

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

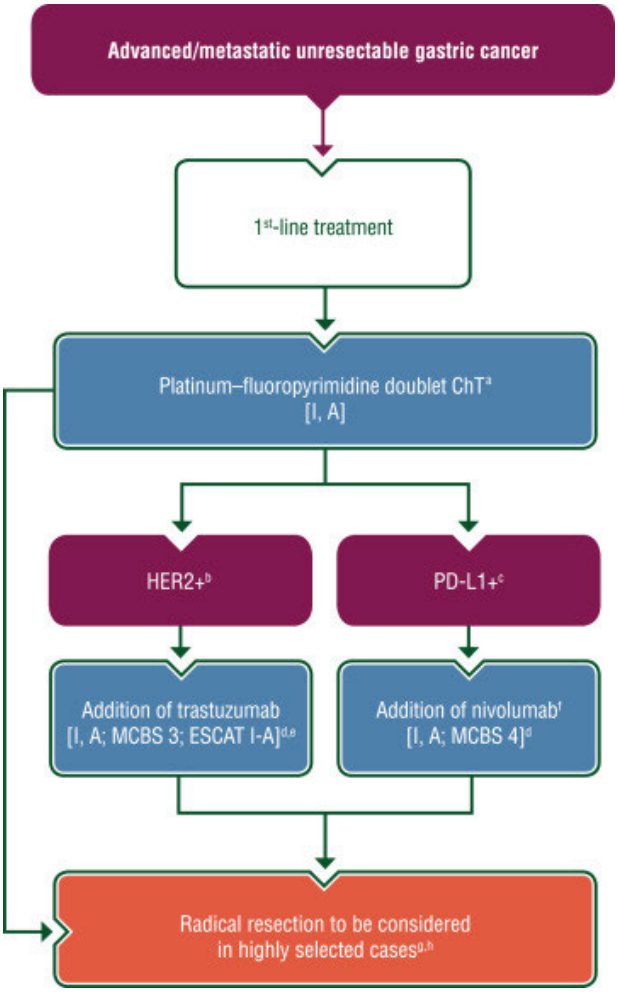
Table 2. Medicinal products licensed in the EU and indicated for the treatment of gastric cancer

INN or common name	Trade name	Licensed indication	Satisfactory method for orphan purpose
First-Line Treatment of Gastric Cancer			
Tegafur, gimeracil and oteracil	Teysuno	In adults for the treatment of advanced gastric cancer when given in combination with cisplatin.	Yes, as it covers the full therapeutic indication of Vyloy

Trastuzumab	Various generic versions	In combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.	No, for HER2-positive patients
Nivolumab	Opdivo	In combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated 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) ≥ 5.	No, as patients have to express PD-L1
Pembrolizumab	Keytruda	KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1). KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated 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 ≥ 1.	No, as patients have to express PD-L1
Capecitabine	Various generic versions	First-line treatment of advanced gastric cancer in combination with a platinum-based regimen.	Yes, as it covers the full therapeutic indication of Vyloy

Docetaxel	Various generic versions	In combination with cisplatin and 5-fluorouracil for the treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for metastatic disease.	No, as it is restricted to metastatic cancer only.
≥Second-Line Treatment of Gastric Cancer			None of them as second line
Ramucirumab	Cyramza	In combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.	
Trifluridine and tipiracil	Lonsurf	Monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.	
Trastuzumab deruxtecan	Enhertu	Monotherapy for treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.	

The sponsor refers to the recently updated ESMO guidelines (Lordick F et al, 2022). Treatment algorithm for first-line treatment of advanced/metastatic unresectable gastric cancer:



Currently recommended first-line therapies for the target patient population of Vyloy of locally advanced unresectable or metastatic gastric cancer include chemotherapy backbone (fluoropyrimidine- and platinum-containing cytotoxic drugs) in combination with therapy depending on HER2 and PD-L1 CPS status.

Fluoropyrimidine- and platinum-containing cytotoxic drugs in first line therapy:

Oxaliplatin and cisplatin are the most commonly used platinum drugs. Both drugs were shown to be equally effective in RCTs.

Commonly used fluoropyrimidines are 5-fluorouracil, capecitabine as well as the fixed-dose combination drug Teysuno (tegafur/gimeracil/oteracil), which contains the fluoropyrimidine tegafur.

Of note, in the sponsors pivotal study SPOTLIGHT zolbetuximab was evaluated in combination with the fluoropyrimidine- and platinum-containing standard regimen mFOLFOX6, which includes 5-fluorouracil and oxaliplatin. In the sponsors second pivotal study GLOW, zolbetuximab was evaluated in combination with the fluoropyrimidine- and platinum-containing standard regimen CAPOX, which includes capecitabine and oxaliplatin. This was accepted by the SAWP/CHMP as a suitable comparator in a protocol assistance procedure

Due to higher levels of toxicity and uncertain survival benefit over recommended doublet regimens, first-line taxane-based triplet chemotherapy is not recommended as a standard approach (Lordick F et al, 2022).

Therapies for HER2 overexpressing cancers in first line:

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 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.

Therapies for PD-L1 positive and HER2 negative cancers in first line:

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 (Opdivo) or pembrolizumab (Keytruda).

Of note, even though a considerable overlap has been reported recently between patients whose tumours express CLDN18.2 and PD L1 (~75% of CLDN18.2 positive patients have tumours which express PD L1 with a CPS ≥ 1 and ~42% of CLDN18.2 positive patients have tumours which express PD L1 with a CPS ≥ 5), about 25% of patients whose tumours express CLDN18.2 have tumours which express PD L1 with a CPS below 1 and who would neither be eligible for treatment with nivolumab nor pembrolizumab (Kubota et al., 2023, ESMO Open. 2023 Feb; 8(1): 100762).

In conclusion: capecitabine and tegafur/gimeracil/oteracil (Teysuno) are considered satisfactory treatments.

Significant benefit

The sponsor focuses the discussion on the biomarker specificity:

Zolbetuximab was clinically developed to treat patients with HER2-negative gastric/GEJ cancer whose tumours are CLDN18.2 positive. CLDN18.2 status can be reliably determined by immunohistochemical methods, thereby facilitating identification of a patient population (patients with CLDN18.2-positive, HER2-negative, locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma) that can benefit from zolbetuximab treatment. The prevalence of tumours that are CLDN18.2 positive has shown consistency in both phase 3 studies, across regions and across demographic/baseline characteristic subgroups, with > 38% CLDN18.2-positivity (≥ 75% cut off) in participants screened for the global phase 3 studies.

Several studies have been conducted to evaluate the correlation of CLDN18.2 expression with other biomarkers. In the studies of [Pellino et al, 2021] and [Kubota et al, 2023], no significant correlation between CLDN18.2 positivity and the expression of biomarkers such as PD-L1, MMRd and HER-2 were observed. These data suggest similar overlap with other relevant therapeutic biomarkers in CLDN18.2-positive and negative tumours in gastric/GEJ cancers.

PD-L1 CPS prevalence has been reported in multiple studies. In CheckMate 649, the prevalence of patients with a PD-L1 CPS ≥ 5 was 60% (955/1581) [Janjigian et al, 2021b] while other studies have described PD-L1 CPS ≥ 5 within a range of 13 to 31% [Fuchs et al, 2022; Schoemig-Markiefka et al, 2021; Yeong et al, 2022]. An ad hoc analysis of PD-L1 CPS expression was performed using the Dako PD-L1 IHC 28-8 pharmDx assay on samples from a subset of randomized patients in SPOTLIGHT and GLOW for whom consented samples were available for testing. In GLOW, 21.9% (63/288) of

CLDN18.2-positive patients had a PD-L1 CPS ≥5 [Xu et al, 2023], and in SPOTLIGHT, 13.2% (41/311) of CLDN18.2-positive patients had a PD-L1 CPS ≥5[Shitara et al, 2023].Therefore, there is a substantial number of patients expressing CLDN18.2 but no other relevant actionable biomarkers, who are thereby currently left with only chemotherapy as a treatment option.

The efficacy of zolbetuximab in combination with chemotherapy was demonstrated in 2 independent, global, randomized, placebo-controlled phase 3 clinical studies in the biomarker selected CLDN18.2-positive, HER2-negative population with locally advanced or metastatic gastric or GEJ adenocarcinoma in the first-line chemotherapy setting by showing a consistent, statistically significant PFS benefit and a statistically significant, clinically meaningful OS benefit. Subgroup analyses were supportive for both PFS and OS across most prespecified subgroups in both phase 3 studies, albeit not consistently. Supportive evidence comes from the open-label randomized phase 2 FAST study that demonstrated a PFS and OS benefit for zolbetuximab plus EOX chemotherapy vs EOX alone. The addition of zolbetuximab to chemotherapy did not negatively affect the HRQoL of the participants as no significant deterioration in time to first confirmed deterioration (TTCD) relative to the placebo arm was detected.

The sponsor does not claim a significant benefit over any defined products but more in general states that there are many patients who are CLDN18.2 positive but lack other relevant actionable biomarkers, who are thereby currently left with only chemotherapy as a treatment option. However, a discussion of significant benefit over chemotherapy is not provided.

A list of questions was sent to the sponsor in relation to the prevalence calculation and the significant benefit.

Comments on sponsor's response to the COMP list of issues

Prevalence:

The sponsor explained that the prevalence estimate of 2.7 cases per 10 000 in the European Union (EU) was based on 5-year prevalence for the year 2020 [Ferlay et al, 2024] and they briefly explained the underlying methodology used by the International Agency for Research on Cancer to get to the estimate.

The sponsor also discovered that the cancer statistics from GLOBOCAN were updated in Feb 2024 with estimates for the year 2022. Based on these more recent data, the prevalence of gastric cancer in EU for 2022 was estimated at 2.2 cases per 10 000 individuals. This was informed by forecasts for incidence (increase of 3.3%) and mortality (increase of 3.5%) for the year 2025 generated by the prediction model in GLOBOCAN (GLOBOCAN data). Therefore, the sponsor now proposes that **2.2 in 10,000** should be used for the prevalence of gastric cancer.

The sponsor also provided information from the European Cancer Information System (ECIS). Based on data from the ECIS, the 5-year prevalence for the year 2020 was estimated at 3.2 cases per 10 000 individuals (ECIS data). The difference may reflect differences in underlying estimates of incidence and mortality and/or different methodological approaches to calculate prevalence. As ECIS only extends to the year 2020, the sponsor considered that the data from GLOBOCAN is more relevant for this application.

Finally, the sponsor also checked the Global Burden of Disease (GBD) study which reported the global, regional and national burden of stomach cancer in 195 countries between 1990 and 2017 through presentation of incidence and mortality (but not prevalence) [GBD, 2020]. The estimates for incidence and mortality from the GBD study tended to be proportionately higher than those from GLOBOCAN. But the sponsor considered that since prevalence is positively associated with both incidence and

disease duration [Tenny & Hoffman, 2023] (and thus inversely associated with mortality), prevalence estimates generated from the GBD study should be broadly similar to those from GLOBOCAN.

COMP discussion and conclusion:

The COMP recognised that there are several limitations to the estimates. Forecasts are generally not used by the COMP, therefore the estimate of 2.2 in 10,000 from the GLOBOCAN data is not considered acceptable. It is also acknowledged that both GLOBOCAN and ECIS report incidence and prevalence for cancer located to the "stomach" which clearly includes more types of malignancies (e.g. gastrointestinal-stromal-tumours (GIST)) than the designated orphan condition of gastric adenocarcinoma and adenocarcinoma of the gastroesophageal junction (GEJ). Therefore, any estimate based on these figures will be an overestimate. The COMP decided to use the indirect method to estimate the prevalence using the relationship between incidence, duration, and prevalence (P = I x D). The ECIS database reports that in 2022, there were 75,184 new cases of stomach cancer within the EU/EEA population. At the same time the EU/EEA population was about 447 million which gives an incidence of 1.68. A duration of 2 years was considered relevant for this this fast-progressing disease which generate an estimate prevalence of 3.36 in 10,000. The figure was rounded down to approximately 3 in 10,000 as the figure of 3.36 was for stomach cancer and not restricted to the gastric carcinoma.

Significant benefit:

The sponsor provided a summary of the results of the two pivotal studies SPOTLIGHT and GLOW and discussed the benefit over the chemotherapy alone.

SPOTLIGHT

Treatment with zolbetuximab plus modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin (mFOLFOX6) demonstrated a statistically significant PFS benefit with 25% reduction in the risk of a participant experiencing a PFS event compared with placebo plus mFOLFOX6 (hazard ratio [HR] = 0.751, 95% CI: 0.598, 0.942; P = 0.0066) [Table 1]. The median PFS was approximately 2 months longer for zolbetuximab plus mFOLFOX6 (10.61 months, 95% confidence interval [CI]: 8.90, 12.48) vs placebo plus mFOLFOX6 (8.67 months, 95% CI: 8.21, 10.28); see [Figure 1] for the corresponding Kaplan-Meier curve. Median follow-up time for PFS was similar in both treatment arms (zolbetuximab plus mFOLFOX6: 12.94 months, 95% CI: 11.63, 15.28; placebo plus mFOLFOX6: 12.65 months, 95% CI: 10.71, 15.24)

At the primary OS analysis, 149 (52.7%) participants in the zolbetuximab plus mFOLFOX6 arm and 177 (62.8%) participants in the placebo plus mFOLFOX6 arm had died. The analysis of OS showed a clinically relevant, statistically significant OS benefit (HR = 0.750, 95% CI: 0.601, 0.936; P = 0.0053), with 25% reduction in the risk of death in participants treated with zolbetuximab plus mFOLFOX6 vs placebo plus mFOLFOX6 [Table 1]. The median duration of OS was approximately 2.7 months longer for zolbetuximab plus mFOLFOX6 (18.23 months, 95% CI: 16.43, 22.90) vs placebo plus mFOLFOX6 (15.54 months, 95% CI: 13.47, 16.53); see [Figure 2] for the corresponding Kaplan-Meier curve.

GLOW

Treatment with zolbetuximab plus capecitabine and oxaliplatin (CAPOX) demonstrated a statistically significant PFS benefit, with 31% reduction in the risk of a participant experiencing a PFS event compared with placebo plus CAPOX (HR = 0.687, 95% CI: 0.544; 0.866; P = 0.0007) [Table 1]. The median PFS was approximately 1.4 months longer for zolbetuximab plus CAPOX (8.21 months, 95% CI: 7.46, 8.84) vs placebo plus CAPOX (6.80 months, 95% CI: 6.14, 8.08); see [Figure 3] for the corresponding Kaplan-Meier curve. Median follow-up time for PFS was similar in both treatment arms

(zolbetuximab plus CAPOX: 12.62 months, 95% CI: 10.32, 15.21; placebo plus CAPOX: 12.09 months, 95% CI: 10.25, 15.05).

At the primary OS analysis, 144 (56.7%) participants in the zolbetuximab plus CAPOX arm and 174 (68.8%) participants in the placebo plus CAPOX arm had died. The analysis of OS showed a clinically relevant, statistically significant (HR = 0.771, 95% CI: 0.615, 0.965; P = 0.0118) 23% reduction in the risk of death in participants treated with zolbetuximab plus CAPOX vs placebo plus CAPOX [Table 1]. The median duration of OS was approximately 2.2 months longer for zolbetuximab plus CAPOX (14.39 months, 95% CI: 12.29, 16.49) vs placebo plus CAPOX (12.16 months, 95% CI: 10.28, 13.67); see [Figure 4] for the corresponding Kaplan-Meier curve.

Table 1 Overview of Efficacy in SPOTLIGHT and GLOW (Full Analysis Set)

	SPOTLIGHT		GLOW	
Parameter	**Zolbetuximab plus mFOLFOX6 (n = 283)**	**Placebo plus mFOLFOX6 (n = 282)**	**Zolbetuximab plus CAPOX (n = 254)**	**Placebo plus CAPOX (n = 253)**
PFS (Assessed by IRC)				
Events, n (%)	146 (51.6)	167 (59.2)	137 (53.9)	172 (68.0)
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)
HR (95% CI)‡	0.751 (0.598, 0.942)		0.687 (0.544, 0.866)	
P value§	0.0066		0.0007	
PFS Rate, % (95% CI)¶				
At 6 months	78.05 (72.43, 82.67)	71.95 (66.03, 77.03)	70.20 (63.42, 75.96)	61.47 (54.82, 67.45)
At 12 months	48.86 (41.92, 55.43)	35.04 (28.45, 41.69)	34.86 (27.75, 42.05)	19.13 (13.50, 25.51)
At 18 months	30.93 (23.83, 38.28)	20.82 (14.48, 27.96)	23.91 (17.09, 31.38)	10.62 (5.68, 17.33)
At 24 months	24.41 (17.36, 32.13)	14.87 (8.78, 22.47)	14.49 (6.17, 26.19)	7.28 (2.99, 14.16)
At 30 months	24.41 (17.36, 32.13)	13.01 (7.07, 20.82)	NE (NE, NE)	7.28 (2.99, 14.16)
Overall Survival				
Deaths, n (%)	149 (52.7)	177 (62.8)	144 (56.7)	174 (68.8)
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)
HR (95% CI)‡	0.750 (0.601, 0.936)		0.771 (0.615, 0.965)	
P value§	0.0053		0.0118	
OS Rate, % (95% CI)¶				
At 12 months	67.69 (61.49, 73.12)	59.97 (53.63, 65.72)	57.54 (50.71, 63.77)	50.79 (44.12, 57.06)
At 18 months	50.46 (43.51, 57.00)	38.05 (31.52, 44.54)	38.10 (30.96, 45.19)	28.14 (21.95, 34.65)
At 24 months	38.77 (31.62, 45.85)	28.38 (22.10, 34.98)	28.92 (21.75, 36.46)	17.38 (11.62, 24.12)
At 30 months	26.95 (19.88, 34.51)	16.19 (10.50, 22.97)	16.01 (7.73, 26.95)	10.87 (5.12, 19.06)
At 36 months	20.86 (13.68, 29.08)	8.74 (3.21, 17.79)	NE (NE, NE)	NE (NE, NE)

All participants were randomized to 1 of the treatment groups (FAS).

Zolbetuximab: 800 mg/m^2 loading dose on Cycle 1, day 1 followed by 600 mg/m^2 on subsequent doses.

CAPOX: capecitabine and oxaliplatin; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; 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.

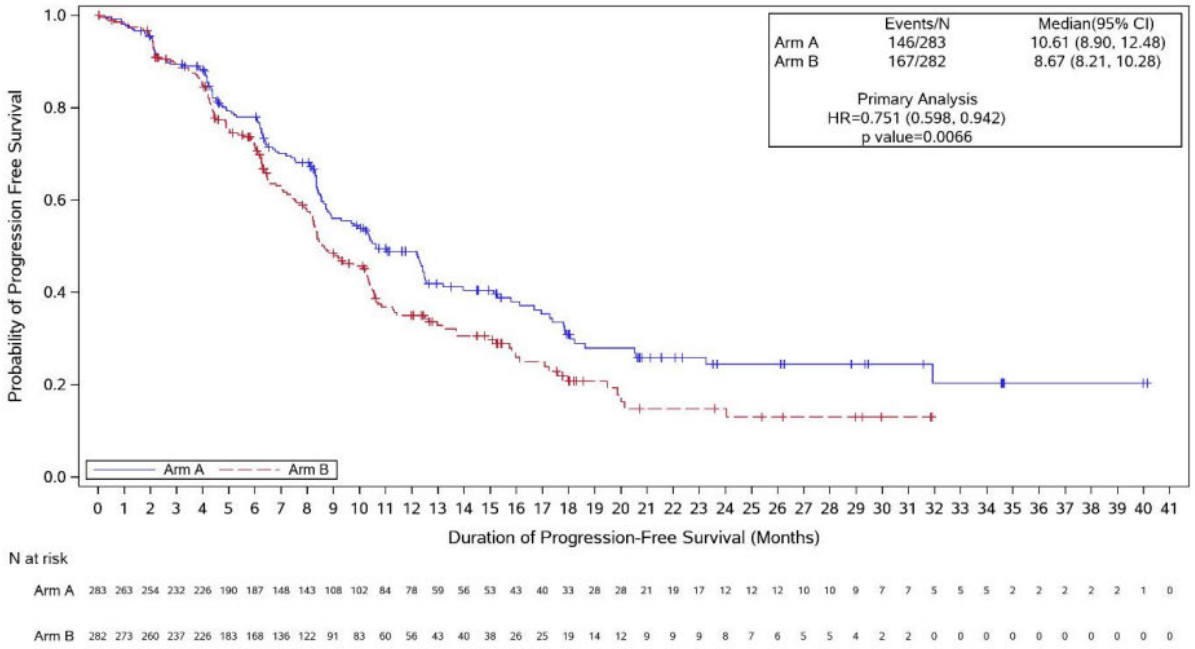
‡ Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites, prior gastrectomy and study ID in the integrated analysis as the explanatory variables. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment group.

§ Based on 1-sided log-rank test.

¶ PFS, OS rate and respective 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Source: [Zolbetuximab Global BLA Module 2.7.3 Table 3, Table 4, Table 8, Table 9]

Figure 1 Kaplan-Meier Plot of PFS Assessed by IRC – FAS (SPOTLIGHT)



Data cutoff: 09 Sep 2022.

All participants were randomized to 1 of the treatment arms (FAS).

Arm A participants received zolbetuximab 800/600 mg/m^2 plus mFOLFOX6; Arm B participants received placebo plus mFOLFOX6.

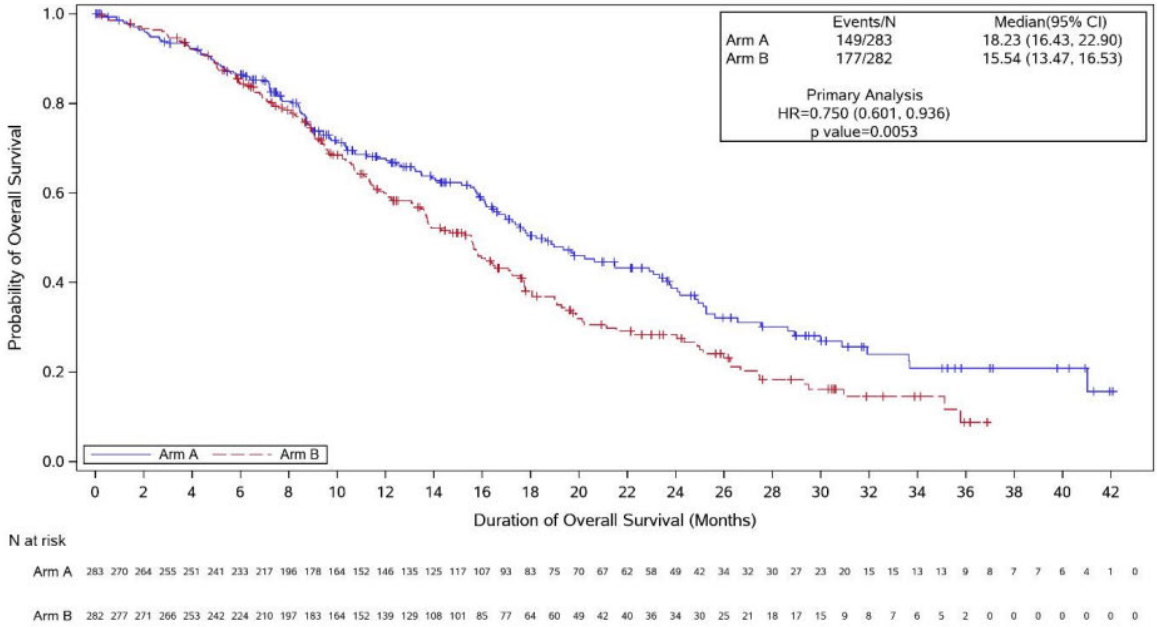
P value is generated from stratified 1-sided log-rank test for the comparison of Arm A and Arm B.

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. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment arm.

CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IRC: independent review committee; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin; PFS: progression-free survival

Source: [Zolbetuximab Global BLA Module 2.7.3 Figure 1]

Figure 2 Kaplan-Meier Plot of Overall Survival – FAS (SPOTLIGHT)



Data cutoff: 09 Sep 2022.

All participants were randomized to 1 of the treatment arms (FAS).

Arm A participants received zolbetuximab 800/600 mg/m^2 plus mFOLFOX6; Arm B participants received placebo plus mFOLFOX6.

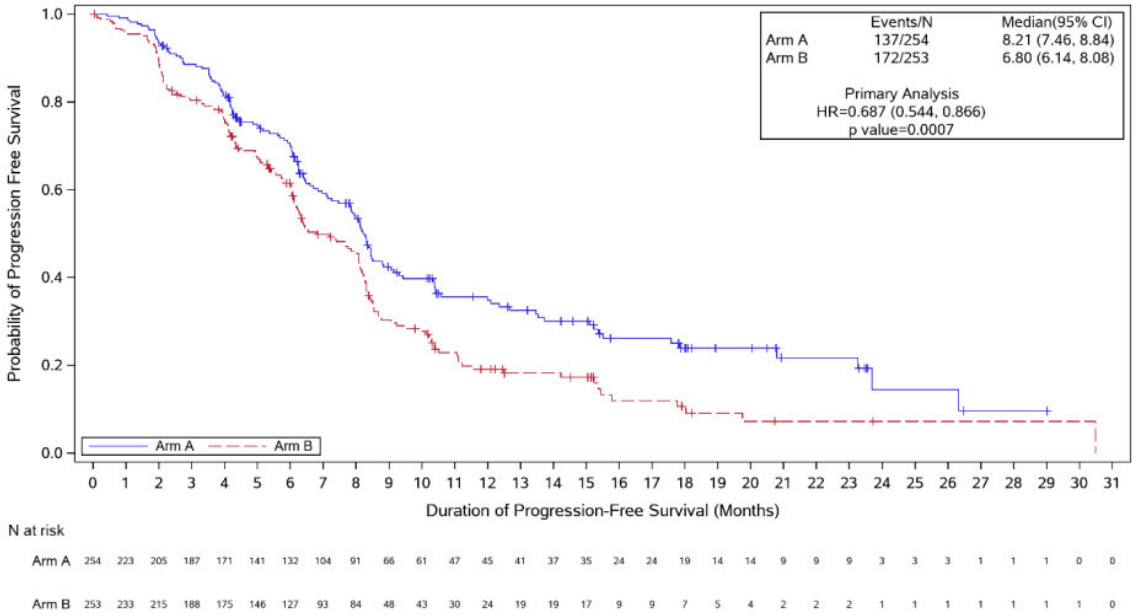
P value is generated from stratified 1-sided log-rank test for the comparison of Arm A and Arm B.

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. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment arm.

CI: confidence interval; FAS: full analysis set; HR: hazard ratio; mFOLFOX6: modified 5-fluorouracil, leucovorin (or folinic acid) and oxaliplatin

Source: [Zolbetuximab Global BLA Module 2.7.3 Figure 3]

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



Data cutoff: 07 Oct 2022.

All participants were randomized to 1 of the treatment arms (FAS).

Arm A participants received zolbetuximab 800/600 mg/m^2 plus CAPOX; Arm B participants received placebo plus CAPOX.

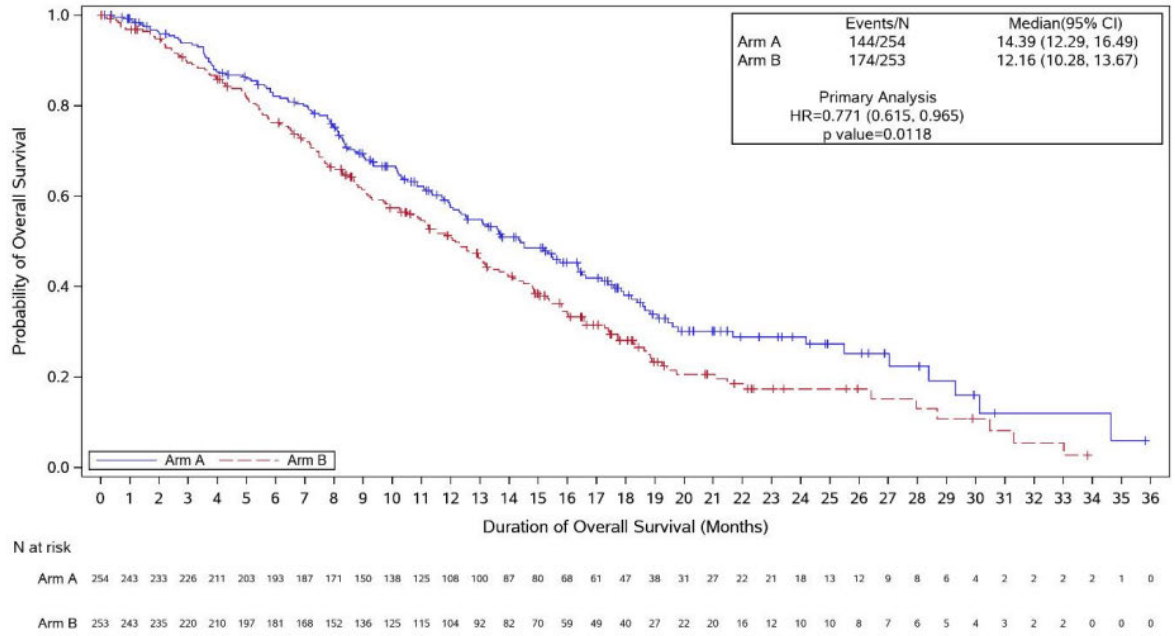
P value is generated from stratified 1-sided log-rank test for the comparison of Arm A and Arm B.

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. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment arm.

CAPOX: capecitabine and oxaliplatin; CI: confidence interval; FAS: full analysis set; HR: hazard ratio; IRC: independent review committee; PFS: progression-free survival

Source: [Zolbetuximab Global BLA Module 2.7.3 Figure 5]

Figure 4 Kaplan-Meier Plot of Overall Survival – FAS (GLOW)



Data cutoff: 07 Oct 2022.

All participants were randomized to 1 of the treatment arms (FAS).

Arm A participants received zolbetuximab 800/600 mg/m^2 plus CAPOX; Arm B participants received placebo plus CAPOX.

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. Assuming proportional hazards, a HR < 1 indicates a reduction in hazard rate in favor of the treatment arm.

CAPOX: capecitabine and oxaliplatin; CI: confidence interval; FAS: full analysis set; HR: hazard ratio

Source: [Zolbetuximab Global BLA Module 2.7.3 Figure 7]

COMP conclusion:

Taken together, these data demonstrate that adding zolbetuximab to first-line chemotherapy (fluoropyrimidine- and platinum-containing chemotherapy) provides a statistically significant PFS benefit as well as a statistically significant and clinically meaningful OS benefit in participants with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma whose tumours are CLDN18.2-positive, and that the observed efficacy is reproducible across independent clinical studies.

4. COMP position adopted on 29 July 2024

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of gastric cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to dysphagia, weight loss and gastric bleeding;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Vyloy, the claim that Vyloy is of significant benefit to those affected by the orphan condition is established. Vyloy in combination with first-line chemotherapy (fluoropyrimidine- and platinum-containing chemotherapy) provides a statistically significant progression free survival benefit as well as an improvement in overall survival in patients with HER2-negative locally advanced unresectable or metastatic gastric or gastro-oesophageal-junction adenocarcinoma whose tumours are CLDN18.2-positive as compared to the chemotherapy alone.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Vyloy, chimeric monoclonal antibody against claudin-18 splice variant 2, zolbetuximab for treatment of gastric cancer (EU/3/10/803) is not removed from the Community Register of Orphan Medicinal Products.