25 July 2019
EMA/479870/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Lonsurf

International non-proprietary name: trifluridine / tipiracil

Procedure No. EMEA/H/C/003897/II/0012

Marketing authorisation holder (MAH): Les Laboratoires Servier

Note

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

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List of abbreviations

Term	Definition
5-FU	5-fluorouracil
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	as-treated
BID	twice per day
BSA	body surface area
BSC	best supportive care
CHMP	committee for medicinal products for human use
CI	confidence interval
CT	consolidated term
CPH	Cox proportional hazards
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
DCR	disease control rate
DMC	data monitoring committee
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DoR	duration of response
ECOG	Eastern cooperative oncology group
EEA	European economic area
EMA	European medicines agency
EORTC	European organisation for research and treatment of cancer
ESMO	European society for medical oncology
EU	European union
EURDs	EU reference dates
FTD	trifluridine
GC	gastric cancer
G-CSF	granulocyte-colony stimulating factor
GCP	good clinical practice
GEJ	gastro-esophageal junction
GVP	good pharmacovigilance practices
HCl	hydrochloride

Term	Definition
HER2	human epidermal growth factor receptor 2
HER2+	HER2-positive
HER2-	HER2-negative
HR	hazard ratio
HR QoL	health-related quality of life
IA	interim analysis
ICH	international conference on harmonisation
ILD	interstitial lung disease
ITT	intention-to-treat
IU	International Units
IXRS	interactive voice/web response system
MA	marketing authorization
MAH	marketing authorization holder
mCRC	metastatic colorectal cancer
mDoR	median duration of response
MedDRA	medical dictionary for regulatory activities
mGC	metastatic gastric cancer
mOS	median overall survival
mPFS	median progression-free survival
MSI-H	microsatellite instability high
NA	not available
NCI CTCAE	national cancer institute common terminology criteria for adverse events
NCCN	national comprehensive cancer network
ORR	objective response rate
OS	overall survival
PDCO	paediatric committee of the European medicines agency
PDT	post-discontinuation anti-cancer therapy
PD-1	programmed cell death 1
PD-L1+	tumours positive for PD-1 ligand
PEC	predicted environmental concentration
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	*per os*, i.e. orally
PR	partial response
PS	performance status
PSUR	periodic safety update report
PT	preferred term
QLQ	QoL questionnaire
QLQ-C30	quality of life questionnaire - core 30
QLQ-STO22	quality of life questionnaire - gastric cancer-specific module
QoL	quality of life

Term	Definition
RCT	randomised controlled trials
RECIST	response evaluation criteria in solid tumours
RECOURSE	refractory colorectal cancer study
RMP	risk management plan
ROW	rest of world
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	stable disease
SOC(s)	system organ class(es)
TAGS	TAS-102 gastric study, i.e. the main/pivotal study
TEAE(s)	treatment-emergent adverse event(s)
TPase	thymidine phosphorylase
TPI	tipiracil hydrochloride
TR	tumour response
ULN	upper limit of normal
US(A)	United States (of America)
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 11 October 2018 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy for Lonsurf; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. An RMP has also been submitted and updated in accordance with Template Rev 2.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 adopted on 23 July 2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Jorge Camarero Jiménez

Timetable	Actual dates
Submission date	11 October 2018
Start of procedure:	3 November 2018
CHMP Rapporteur Assessment Report	20 December 2018
CHMP Co-Rapporteur Assessment Report	20 December 2018
PRAC Rapporteur Assessment Report	3 January 2019
PRAC members comments	9 January 2019
Updated PRAC Rapporteur Assessment Report	10 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	21 December 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 January 2019
Request for supplementary information (RSI)	31 January 2019
CHMP Rapporteur Assessment Report	28 May 2019
PRAC Rapporteur Assessment Report	3 June 2019
PRAC members comments	5 June 2019
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	14 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur Assessment Report	21 June 2019
2nd Request for Supplementary Information	27 June 2019
PRAC Rapporteur's updated assessment report circulated on:	09 July2019
PRAC members comments	15 July2019
Updated PRAC Rapporteur Assessment Report	n/a
CHMP members comments	15 July 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	n/a
CHMP opinion:	25 July 2019

2. Scientific discussion

2.1. Introduction

Lonsurf (trifluridine/tipiracil)

Lonsurf (trifluridine/tipiracil, also named TAS-102 or S95005) is comprised of trifluridine (FTD; an antineoplastic thymidine-based nucleoside analogue), and tipiracil hydrochloride (TPI; a thymidine phosphorylase (TPase) inhibitor), at a molar ratio 1: 0.5. Following uptake into cancer cells, FTD is phosphorylated by thymidine kinase. Subsequently, this compound is further metabolised in the cells to a deoxyribonucleic acid DNA substrate. This substrate is incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, FTD is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, TPI. In non-clinical studies, TAS-102 demonstrated antitumour activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of TAS-102 against several human tumour xenografts correlated highly with the amount of FTD incorporated into DNA, suggesting this as the primary mechanism of action.

In the European Union (EU), Lonsurf is approved for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. The recommended starting dose of Lonsurf is 35 mg/m^2/dose administered orally twice daily (BID) on days 1 to 5 and days 8 to 12 of each 28-day cycle, which is to be continued as long as benefit is observed or until unacceptable toxicity occurs.

Lonsurf has been administered, alone or in combination with other agents, to at least 4,000 patients in clinical trials, and to more than 64,000 patients worldwide (of which 16,173 in Europe) as a marketed product.

Indication applied for in current procedure

The MAH initially applied for the following new indication:

Gastric cancer

Lonsurf is indicated for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy.

The following indications have been agreed:

Colorectal cancer

*Lonsurf is indicated **as monotherapy** for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.*

Gastric cancer

Lonsurf is indicated as 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 (see section 5.1).

At the time of submission Lonsurf was not approved for the treatment of gastric cancer in any region (during the procedure it has received approval in the USA on the 22 February 2019).

The proposed posology for the treatment of gastric cancer is the same as for the currently approved mCRC indication, i.e. 35 mg/m^2 administered BID *per os* (PO) on days 1 to 5 and days 8 to 12 of each 28-day cycle, which is to be continued as long as benefit is observed or until unacceptable toxicity occurs.

The addition of *monotherapy* for both indications is introduced for clarity and consistency with the regulatory approach in the field after discussion at the oncology working party which approved that product used as monotherapy in clinical practice should always specify this in the indication.

Gastric cancer

Gastric cancer (GC; also referred to as stomach cancer), is the fifth most common and third most deadly cancer in the world. In 2018, there were over 1 million (1,033,701) new cases of GC and 782,685 deaths from GC reported globally. Of these, 133,133 cases and 102,167 deaths occurred in the EU. The geographic distribution of GC, is varied across the globe, with the highest burden of disease seen in Eastern and Western Asia, Central and Eastern Europe, and South America (Globocan 2018; accessed on 21 November 2018).

Gastro-oesophageal junction (GEJ) cancer anatomically straddles the distal oesophagus and proximal stomach. Due to its location and given that, like GC, the majority of GEJ tumours are adenocarcinomas, GEJ cancer is frequently grouped together with GC in the advanced setting and treated the same way. For simplicity, when hereafter the term "GC" is used, this includes both gastric as well as GEJ cancer, unless stated otherwise.

Surgical resection is available as a potentially curative option for patients diagnosed with early stage disease, although the majority of patients will ultimately relapse following resection (Smyth, 2016). Approximately half of patients will have advanced disease, not eligible for resection, at diagnosis (Ajani, 2016).

Advanced and/or metastatic gastric cancer (i.e. stage IV) remains among the deadliest solid tumours, with 5-year overall survival (OS) below 5%; even with optimal treatment, median survival remains less than 1 year (Yang, 2011; Digklia, 2016; Koizumi, 2008). Patients with inoperable advanced and/or metastatic disease should be considered for chemotherapy, which has shown improved survival and quality of life compared with best supportive care alone (Smyth, 2016).

The most common therapeutic approach in *first-line systemic treatment* for these patients is doublet chemotherapy, most commonly employing a fluoropyrimidine and a platinum derivative (Ajani, 2016; Smyth, 2016). Evidence suggests that significant benefit may derive from the addition of a third agent (for example, docetaxel), provided the patient is able to tolerate such treatment (Okines, 2009). For patients with human epidermal growth factor receptor 2-positive (HER2+) tumours (approximately 20% [van Cutsem, 2015]), the addition of trastuzumab is recommended (Smyth, 2016).

For patients who progress following first-line chemotherapy, *second-line treatment* has been shown to further prolong survival and improve quality of life for many patients. Selection of treatment is dependent upon prior therapy and performance status (PS) at baseline. The European Society for Medical Oncology (ESMO) guidelines currently provide a number of possible approaches that may include the anti-vascular endothelial growth factor receptor monoclonal antibody ramucirumab and/or paclitaxel, irinotecan, or docetaxel (Smyth, 2016).

After failure of second-line therapies, there are neither approved nor standard third-line treatments. Nevertheless, patients with good PS (≤1) and with good organ function could be offered the option to receive systemic chemotherapy without proof of OS benefit. Indeed, even though currently not supported by randomized data, third-line chemotherapy is increasingly administered to patients failing previous lines and maintaining an acceptable PS, particularly in Asian countries (Salati, 2017). Then again, the ESMO

guidelines note on this matter that second-line treatment options may be used sequentially in second- and third- line, but with caution that "there is no clear evidence for a benefit beyond second-line treatment" (Smyth, 2016).

As said, no study has yet identified a preferred or consistently effective third- (or later-) line option for all patients, although apatinib and nivolumab have shown success for different subsets of patients (Li, 2016; Kang, 2017). The major concern for the results of these product is the lack of generalisability to a European population since both medicinal products' studies enrolled only Asian patients, who are recognised to have different tumour biology and clinical outcome compared to the European population. Apatinib and nivolumab are not registered in the EU for this indication. Very recently, the results of the JAVELIN Gastric 300 study of avelumab versus (vs.) physician's choice of paclitaxel or irinotecan as third-line treatment in metastatic gastric cancer (mGC) were published. The study did not meet its primary objective of superiority in OS (Bang, 2018).

Considering the above, best supportive care (BSC) is deemed an acceptable option for the target population.

Table 1 provides an overview of the main randomised controlled trials (RCT) in second- and later-line treatment of mGC. From the rather poor efficacy outcomes in this table, it is clear that new therapeutic approaches are urgently needed in this setting.

Table 1. Post-second-line treatment of metastatic gastric cancer - Overview of randomised controlled trials

Citation Trial Type (Phase)	Trial Description	Efficacy Outcomes
Kang, 2012 RCT (Phase 3) N=202	Docetaxel or irinotecan plus BSC vs. BSC alone (South Korea) ≥2nd line	mOS 5.3 vs. 3.8 months (p=0.007) mPFS: NR ORR: 9.5% vs. NR
Shitara, 2018 RCT (Phase 3) N=395	KEYNOTE-061: Pembrolizumab vs. paclitaxel ≥2nd line	OS: 9.1 vs. 8.3 months (NS) PFS: 1.5 vs. 4.1months
Li, 2016 RCT (Phase 3) N=267	Apatinib vs. placebo (China) 3rd line	mOS: 6.5 vs. 4.7 months (p=0.0156) mPFS: 2.6 vs. 1.8 months ORR: 2.8% vs. 0%
Kang, 2017 RCT (Phase 3) N=493	ATTRACTION-2: nivolumab vs. placebo (Japan, South Korea, Taiwan only) ≥3rd line	mOS: 5.3 vs. 4.1 months (p<0.0001) mPFS: 1.6 vs. 1.5 months ORR: 11.2% vs. 0%
Bang, 2018 RCT (Phase 3) N=371	JAVELIN Gastric 300; Avelumab vs. chemotherapy (paclitaxel or irinotecan) 3rd line	mOS: 4.6 vs. 5.0 months (NS) mPFS: 1.4 vs. 2.7 months ORR: 2.2% vs. 4.3%

Abbreviations: BSC = best supportive care; N = number of patients in trial; NS = not Statistically significant; ORR = objective response rate; mOS = median overall survival; mPFS = median progression-free survival

TAS-102 in treatment-refractory metastatic gastric cancer

The efficacy of TAS-102 against tumours insensitive to 5-FU has been demonstrated, both *in vitro* and *in vivo,* using a variety of human gastric carcinoma models (Matsuoka, 2018; Suzuki, 2017).

TAS-102 has previously been evaluated in the treatment of patients with GC in two separate clinical studies.

The first was study TAS-102-9806, an open-label, single-arm (Taiho-sponsored) study conducted in the US, in which patients with mGC who had progressed on 1 prior therapy received TAS-102 monotherapy 25

mg/m^2 BID (thus a lower dose than the approved dose of 35 mg/m^2 BID in colorectal cancer). The study design was the 2-stage Simon design and there was no tumour response among the first 18 patients in stage 1; accordingly, this study was terminated early and did not proceed to stage 2. Safety findings were consistent with the safety profile of TAS-102 established in earlier pivotal mCRC clinical studies (Mayer, 2015, i.e. page 25-6 of RECOURSE protocol in Supplementary Material).

The second study, EPOC1201 (Bando, 2016), was an investigator-initiated Phase 2 study conducted in Japan, evaluating the efficacy and safety of TAS-102 (35 mg/m^2 BID) in 29 patients with treatment-refractory mGC who had previously received 1 or 2 previous chemotherapy regimens containing fluoropyrimidines, platinum agents, and taxanes or irinotecan. In this study, the objective response rate (ORR) was 3.4% (95% confidence interval [CI], 0.1, 17.8), the disease control rate (DCR) was 65.5% (95% CI, 45.7, 82.1); the median progression-free survival (PFS) was 2.9 months (95% CI, 1.1, 5.3) by investigator assessment, and median OS (mOS) was 8.7 months (95% CI, 5.7, 14.9). In this population of pre-treated patients, TAS-102 had an acceptable toxicity profile. Common Grade 3 or 4 adverse events (AEs) included neutropenia (69.0%), leukopenia (41.4%), anaemia (20.7%) and anorexia (10.3%). No treatment-related deaths were observed.

The results of study EPOC1201, which included DCR, mOS, and median PFS (mPFS) comparable to or better than those achieved in other studies of post-second-line treatment approaches to mGC (Table 1), provided the rationale for the pivotal study that forms the basis of this application, i.e. the randomized, placebo-controlled, phase 3 TAS-102 gastric study (TAS-102-302, TAGS). Of note, the results of TAGS have very recently been published (Shitara, 2018).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In light of the extension of the indication for Lonsurf, an environmental risk assessment was submitted by the MAH.

In the new proposed indication considering the worst case situation for the daily dose calculation and the revised prevalence of Gastric cancer, the $PEC_{SURFACEWATER}$ (µg/L) for trifluridine and tipiracil, HCl can be calculated as follow for gastric cancer:

PECSURFACEWATER for trifluridine = 57.14x1000x0.0000259 / 200x10 = 0.00074 µg/L
PECSURFACEWATER for tipiracil, HCl = 23.39x1000x0.0000259 / 200x10 = 0.00030 µg/L

Calculation taking into consideration both indications, metastatic colorectal cancer and gastric cancer, for Lonsurf provides a $PEC_{SURFACEWATER}$ of:

PECSURFACEWATER (µg/L) for trifluridine = 0.0029 + 0.00074 = 0.0036 µg/L
PECSURFACEWATER (µg/L) for tipiracil, HCl = 0.0012 + 0.00030 = 0.0015 µg/L

Based on the calculation above a Phase II assessment is not necessary.

2.2.2. Conclusion on the non-clinical aspects

Trifluridine-tipiracil HCl is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial (Table 2) was performed in accordance with GCP as claimed by the applicant.

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

Table 2. Tabular overview of clinical study

Study ID	Description	Treatment	Number of patients	Endpoints
TAS-102-302 (TAGS)	Randomized, double-blind, placebo-controlled, phase 3 study in patients with mGC who have received ≥2 prior regimens (including fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumours are known to be HER2+ were required to have received prior anti-HER2 therapy if available) and were refractory to or failing those chemotherapies	TAS-102 35 mg/m^2 PO BID on days 1 to 5 and days 8 to 12 of each 28-day cycle + BSC or placebo + BSC	N=507 patients (ITT population) TAS-102: 337 Placebo: 170	**Primary**: • OS **Key secondary**: • PFS, safety and tolerability **Other secondary**: • ORR, DCR, time to deterioration of ECOG PS to ≥2, QoL

Abbreviations: BID = twice daily; BSC = best supportive care; mGC = metastatic gastric cancer; DCR = disease control rate; ECOG: Eastern cooperative oncology group; HER2+: human epidermal growth factor receptor 2-positive; ITT = intent to treat; ORR = overall response rate; OS = overall survival; PS: performance status; PFS = progression free survival; PO = by mouth; QoL: Quality of life

2.3.2. Pharmacokinetics

No pharmacokinetic (PK) assessments were conducted during study TAS-102-302 (TAGS). Further, drug-drug and drug-disease (non-cancer) interactions were not evaluated in this study.

The proposed TAS-102 starting dose in adult patients with mGC is 35 mg/m^2 administered orally twice daily (BID) on days 1 to 5 and days 8 to 12 of each 28-day cycle, which is to be continued as long as benefit is observed or until unacceptable toxicity occurs. This posology is identical to that previously accepted for treatment of adult patients with mCRC. No specific comparison of the PK of FTD and/or TPI between mGC and mCRC patient types was provided in this variation. However, in the initial application for the mCRC indication, TAS-102 was dosed to patients with various solid tumours. No differences in PK of FTD and/or TPI were noted between the different patient populations at that time (Lonsurf mCRC EPAR).

2.3.3. Pharmacodynamics

Not applicable, as no new data were provided in this application.

2.3.4. Conclusions on clinical pharmacology

There are no indications that FTD and/or TPI Pharmacology in mGC patients is different to that in mCRC patients.

2.4. Clinical efficacy

The only study included in this application, is the pivotal study (TAGS).

2.4.1. Dose response study(ies)

No dose response studies were included in this application. The applicant has given a justification for the proposed posology as follows:

TAS-102 (35 mg/m2/dose) was administered orally BID, within 1 hour after completion of morning and evening meals, for 5 days each week with 2 days rest for 2 weeks, followed by a 14-day rest. This treatment cycle was repeated every 4 weeks. The safety and tolerability of this TAS-102 regimen was previously demonstrated in the randomized, double-blind, phase 3 study (RECOURSE; TPU-TAS-102-301), in which TAS-102 was shown to significantly improve OS compared to placebo in patients with mCRC, who had previously been treated with, or were not candidates for fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-epidermal growth factor receptor (EGFR) therapy (Mayer, 2015; Lonsurf mCRC EPAR). In an investigator-sponsored, phase 2 study conducted in Japan (Bando, 2016), this TAS-102 regimen was also well-tolerated in patients (n = 29) with mGC who had failed prior standard therapies.

In addition, a lower dose of 25 mg/m^2 BID was investigated as second-line treatment in the other phase 2 study TAS-012-9806 in US patients with mGC. As there was no tumour response among the patients in stage 1 of the 2-stage Simon study design, this study was terminated early (Mayer 2015).

2.4.2. Main study

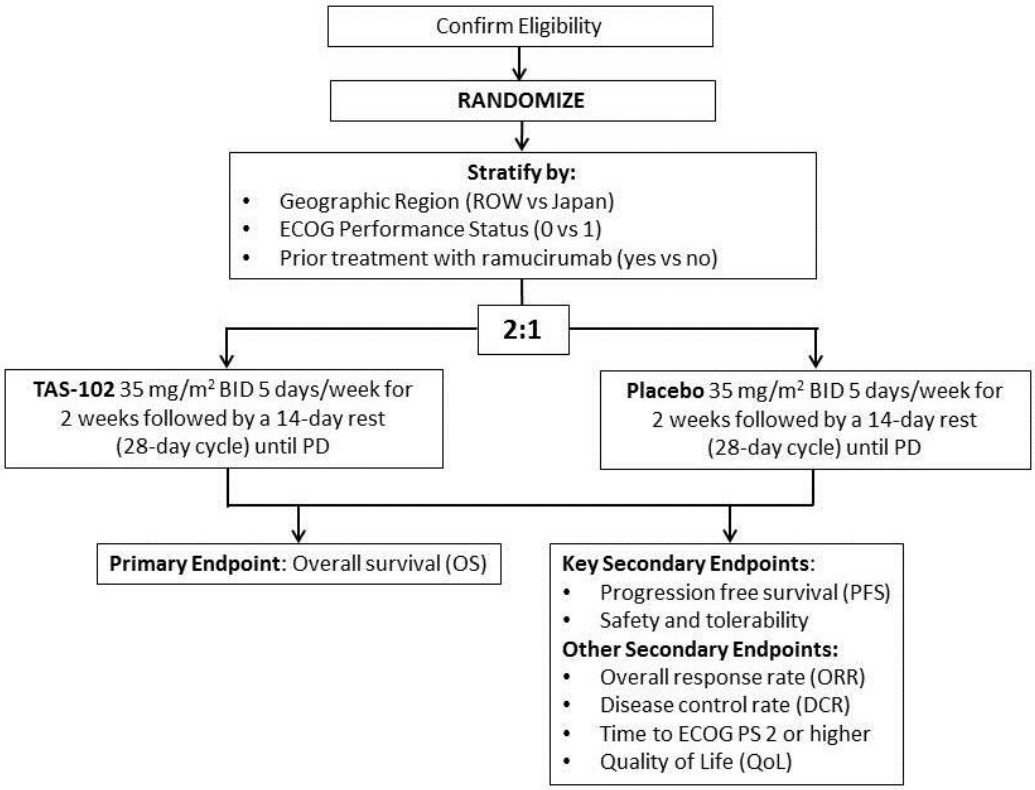
Title of Study

TAGS (TAS-102-302): Randomized, Double-Blind, Phase 3 Study Evaluating TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Gastric Cancer Refractory to Standard Treatments

Methods

TAGS was a multinational, randomized, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of TAS-102 plus Best Supportive Care (BSC) vs. placebo plus BSC in patients with mGC refractory to standard treatments, i.e. patients who had received ≥2 prior regimens for advanced disease and were refractory to or unable to tolerate their last prior therapy. A schematic of the study design is provided in Figure 1.

Figure 1. Study design TAGS



Abbreviations: BID = twice daily; ECOG = Eastern cooperative oncology group; PD = progressive disease; PS = performance status; ROW = rest of world

Eligible patients who met all of the inclusion and none of the exclusion criteria (see below in section **Study participants**) were centrally randomized (in a 2:1 ratio) to receive either TAS-102 35 mg/m^2 BID per os (PO) plus BSC (experimental arm) or placebo plus BSC (control arm).

Computed tomography (CT) scans were performed at baseline (i.e. within 28 days prior to day 1 of cycle 1) and every 8 weeks thereafter until disease progression. On-site tumour assessments were performed by the investigator/local radiologist. Tumour assessments were analysed using response evaluation criteria in solid tumours (RECIST) criteria (version 1.1, 2009). Patient reported quality of life assessments (EORTC QLQ-C30 and QLQ-STO22) were performed prior to study treatment administration in each cycle.

For patients who discontinued treatment for reasons other than radiologic disease progression (e.g., due to intolerable side effects), every effort was made to perform an end of treatment tumour assessment prior to the start of new anti-cancer therapy. These patients continued to be followed for tumour response every 8 weeks until radiologic disease progression (or death) or initiation of new anti-cancer therapy (whichever occurred first). After discontinuation of study treatment, all patients were followed for survival every 4 weeks until death or until the target number of events (deaths) was met, unless a patient had withdrawn consent to participate in the study.

After the final analysis for the primary endpoint of OS, the study was to be unblinded, and patients from the placebo arm were to be offered the option to cross over to open-label TAS-102.

A data monitoring committee (DMC) was established for this study to provide additional, independent oversight that could enhance safety of study participants and the study conduct. The DMC comprised of clinicians and a statistician, all independent from the sponsor and investigative sites and selected as to avoid conflict of interest.

Study participants

The study was conducted at 110 centres in 17 countries: Italy, USA, Turkey, France, Japan, Portugal, UK, Israel, Spain, Russian Federation, Czech Republic, Germany, Poland, Belarus, Belgium, Ireland, and Romania.

Key inclusion criteria were:

1. Adult patients (≥18 years of age), with Eastern cooperative oncology group (ECOG) PS 0 or 1, and who were able to take medications orally.
2. Histologically confirmed, non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction as defined by the American Joint Committee on Cancer (AJCC) staging classification (7th ed., 2010). Documentation of histology of the tumour (primary or metastasis) was required prior to enrolment. Gastroesophageal junction involvement was documented by endoscopic, radiologic, surgical, or pathology report.
3. Patients had previously received ≥2 prior regimens (≥1 cycle per regimen) for advanced disease and patients were refractory to or unable to tolerate their most recent prior therapy:
    a. Prior regimen(s) were required to have included a fluoropyrimidine-, platinum-, and either a taxane- and/or irinotecan-containing regimen; patients whose tumours were HER2+ were required to have received prior anti-HER2 therapy if available.
    b. Patients had progressed based on imaging during or within 3 months of the last administration of their most recent prior regimen.
    c. Patients who had withdrawn from their most recent prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease were also eligible to enter the study.
    d. Patients who received (both preoperative neoadjuvant chemotherapy as well as) postoperative adjuvant chemotherapy or chemo-radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count this therapy as 1 prior regimen for advanced disease (only if the same regimen was administered both pre- and postoperatively).
4. Measurable or non-measurable disease as defined by RECIST 1.1 criteria.
5. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥1,500/mm^3 (i.e., ≥1.5 × 10^9/L by International Units [IU]).
    b. Platelet count ≥100,000/mm^3 (IU: ≥100 × 10^9/L).
    c. Haemoglobin value of ≥9.0 g/dL.
    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × upper limit of normal (ULN); if liver function abnormalities were due to underlying liver metastasis, AST and ALT ≤5 × ULN.
    e. Total serum bilirubin of ≤1.5 × ULN.
    f. Serum creatinine ≤1.5 mg/dL.

Key exclusion criteria were:

1. Previous treatment with TAS-102 and/or known or assumed hypersensitivity to TAS-102 or any of its ingredients.
2. Any serious illness or medical condition(s) including, but not limited to the following:
    a. Other concurrently active malignancies excluding malignancies that were disease-free for more than 5 years or carcinoma-in-situ deemed cured by adequate treatment.
    b. Known brain metastasis or leptomeningeal metastasis.
    c. Active infection.
    d. Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder.
    e. Uncontrolled diabetes.
    f. Myocardial infarction within 12 months prior to randomization, severe/unstable angina, symptomatic congestive heart failure New York Heart Association class III or IV.
    g. Gastrointestinal haemorrhage (Grade ≥3) within 2 weeks prior to randomization.
    h. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or chronic or acute hepatitis B or hepatitis C.
    i. Patients with autoimmune disorders or history of organ transplantation who required immunosuppressive therapy.
3. Any of the following within the specified time frame prior to randomization:
    a. Major surgery within prior 4 weeks.
    b. Any anti-cancer therapy within prior 3 weeks.
    c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks.
    d. Any investigational drug/device received within prior 4 weeks.
3. Any unresolved toxicity NCI CTCAE Grade ≥2, attributed to any prior therapies (excluding anaemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
4. For women: pregnancy or lactation.

Treatments

A treatment cycle was defined for all patients as 28 days. On days 1 through 5 and days 8 through 12 of each cycle, each patient received one of the following treatments (based on the treatment group to which they were randomised). In addition, all patients received BSC.

- Interventional arm: TAS-102 35 mg/m^2 BID PO, within 1 hour after completion of morning and evening meals;
- Control arm: placebo.

TAS-102 contains FTD and TPI as active ingredients with a molar ratio of 1:0.5, and is formulated as an immediate-release film-coated tablet, which is supplied in 2 strengths (expressed as FTD content):

- The '15 mg' white, round tablet contains 15 mg FTD and 6.14 mg TPI (i.e. 7.065 mg TPI HCl) as active ingredients;

- The '20 mg' pale-red, round tablet contains 20 mg FTD and 8.19 mg TPI (i.e. 9.42 mg TPI HCl) as active ingredients.

Placebo tablets had a similar composition to the TAS-102 tablets, except for the active ingredients.

The study drug tablet calculation is presented in Table 3, which shows the number of tablets that are needed per calculated body surface area (BSA).

Table 3. Study drug tablet calculation

TAS-102 dose (twice daily)	Body surface area (m^2)	Dose in mg (twice daily)	Total daily dose (mg)	Tablets per dose (twice daily)	
				15 mg	20 mg
35 mg/m^2	<1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥2.30	80	160	0	4

Study treatment was started within three calendar days after the date of randomization and continued until one of the discontinuation criteria was met or until completion of the primary endpoint, whichever occurred first. The discontinuation criteria included:

- RECIST-defined disease progression;
- Clinical progression;
- An irreversible, treatment-related, Grade 4, clinically relevant, non-hematologic event or (otherwise) unacceptable AE(s), or change in underlying condition such that the patient can no longer tolerate therapy;
- Patient request; and
- Physician's decision.

After the final analysis for OS and unblinding of the study, patients from the placebo arm were to be offered the option to cross over to open-label TAS-102, and patients already receiving TAS-102 were also switched to open-label TAS-102.

Objectives

Primary objective

The primary objective of this study was to evaluate OS for TAS-102 vs. placebo.

The null and alternate hypotheses are read as follows:

- H_0: active treatment does not have a differential effect on the primary assessment of mortality risk (OS hazard ratio [HR]). The null hypothesis presumes that no statistically significant difference in OS between two groups of patients (investigational drug and placebo-controlled) is observed in the study.
- H_A: active treatment does have a differential effect on the primary assessment of mortality risk (OS HR). The alternate hypothesis presumes that there is a statistically significant difference in OS between two groups of patients (investigational drug and placebo-controlled).

Key secondary objectives

The key secondary objectives were:

- Progression-free survival (PFS) based on investigator assessment of radiologic images
- Safety and tolerability

Other secondary objectives

Other secondary objectives were:

- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to deterioration of ECOG PS to a score ≥2
- Quality of life (QoL) as evaluated by the European organization for research and treatment of cancer (EORTC) quality of life questionnaire-core 30 (QLQ-C30) and the QLQ-STO22, which is a module specific to patients with gastric cancer

Outcomes/endpoints

Primary endpoint

OS was the primary endpoint of this study, defined as the time from the date of randomization to the date of death due to any cause for the ITT population. In the absence of confirmation of death or for patients alive as of the OS cut-off date, the survival time was censored at the date of last study follow-up or the cut-off date, whichever was earlier. The cut-off date for OS was to be defined by the date of the 384^{th} death. Patients having a documented survival status (alive or dead) after this date were censored at the cut-off date.

Key secondary endpoints

PFS was defined as the time from the date of randomization until the first date of investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no disease progression as of the analysis cut-off date were censored at the date of the last tumour assessment. Patients who received non-study cancer treatment before disease progression were censored at the date of the last evaluable tumour assessment before the non-study cancer treatment was initiated.

Standard **safety and tolerability** monitoring was performed and AEs were Graded using NCI CTCAE version 4.03.

Other secondary endpoints

The assessment of **ORR** was based on investigator review of radiologic images and following RECIST criteria (version 1.1, 2009). ORR was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR). The assessment of ORR was restricted to the tumour response (TR)

population, i.e. patients with measurable disease (at least 1 target lesion) at baseline and with at least 1 post-baseline evaluation. At the analysis stage, the best overall response was assigned for each patient as the best response recorded from the start of treatment through the treatment period (excluded assessments during follow-up). If applicable, responses recorded after radiologic disease progression or after initiation of non-study antitumor therapy were excluded. A best response assignment of stable disease (SD) required that SD be maintained for at least 6 weeks from the start of treatment.

DCR was defined as the proportion of patients with a best overall response of CR, PR, or SD. The assessment of DCR paralleled that of ORR.

The **time to deterioration to ECOG PS ≥2** was defined as the time from randomization until the first date on which an ECOG PS ≥2 was observed. Of note, ECOG PS 2 entails that a patient is ambulant and capable of all self-care but unable to carry out any work activities. Patients not reaching an ECOG PS score of ≥2 were censored at the last recorded ECOG assessment.

QoL was assessed using the EORTC QLQ-C30 and QLQ-STO22. The core questionnaire, the QLQ-C30, incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The gastric cancer module (QLQ-STO22) is meant for use among gastric cancer patients varying in disease stage and treatment modality. This 22-item instrument is used alongside the 30-item QLQ-C30 core questionnaire, resulting in a total of 52 items. The **time to deterioration of QoL** was defined as the time from randomization until the first date on which a deterioration of QoL by ≥5 points in global health status was observed.

Sample size

The study was designed to detect with 90% power a hazard ratio for death of 0.70 (30% risk reduction) in the TAS-102 arm compared with the placebo arm with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate was assumed. Using a treatment allocation of 2:1 (TAS-102:placebo) of 500 patients, 384 deaths were targeted for the final OS analysis.

Based on these design operating characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target events milestone would be reached approximately 8 months after the last patient was randomized in the study. The mOS in the control arm was estimated based on the observed mOS of 3.8 months in the placebo arm of the phase 3 ramucirumab (REGARD) study in the second-line treatment of GC (Fuchs, 2013), and the observed mOS of 4.3 months in the placebo arm of the phase 3 everolimus (GRANITE) study in the second- and third-line treatment of GC (Ohtsu, 2013). The estimate was further increased to 5 months to account for the higher control median projected in the Japanese population.

One interim analysis (IA) for efficacy and futility was planned for the study after approximately half of the total target events are observed (192 deaths), see section *Statistical methods* below.

Randomisation

Once patient confirmation of eligibility and the criteria for randomization were met, patients were centrally randomized in a 2:1 ratio to TAS-102 plus BSC or placebo plus BSC via an interactive voice/web response system (IXRS) based on a dynamic allocation method (biased coin).

Patients were stratified by the following criteria:

- Region (rest of world [ROW] vs. Japan)

- ECOG PS (0 vs. 1)
- Prior treatment with ramucirumab (yes vs. no)

Blinding (masking)

This was a double-blind study. TAS-102 tablets of each strength, 15 mg or 20 mg, and the corresponding placebo tablets, respectively, were identical in appearance and were packaged in identical containers. During the conduct of the study, the treatment assignment was unknown to all patients, investigators, and ancillary study personnel at each study site, and to employees of the sponsor, except for pre-specified personnel involved in pharmacovigilance reporting activities and clinical trial material management. Among the contract research organizations who assisted in the conduct of the study, treatment assignment was unknown except for personnel involved in drug labelling and distribution, IXRS activities, pharmacovigilance reporting activities, and provision of data for periodic DMC review.

The final analysis was to be performed after the target number of events was reached, i.e. 384 deaths. After the final analysis, the study was to be unblinded. If the primary endpoint of the study was met and efficacy as well as safety supported a favourable benefit/risk ratio for TAS-102, patients currently or previously treated with placebo who continued to meet study eligibility criteria were to be offered the option to cross over to open-label TAS-102. Patients receiving TAS-102 were also switched to open-label TAS-102.

Statistical methods

Analysis populations

The "*intent-to-treat (ITT) population*" comprised all randomized patients, regardless of whether or not study drug was administered. This population was the primary population for the analysis of the efficacy data. All analyses using this population were based on the treatment assigned.

The "*as-treated (AT) population*" was defined as all patients who received at least one dose of study medication. This population was used in the assessment and reporting of safety data. The "as-treated population" was equivalent to "safety population". This population was used for safety analyses. All analyses using this population were based on the treatment actually received.

The "*tumour response (TR) population*" included all patients in the ITT population that met both of the two following criteria:

- measurable disease (at least one target lesion) at baseline; and
- at least one post-baseline evaluation or early disease progression/cancer-related death occurred before first evaluation on treatment (post-baseline) took place.

All analyses using this population were based on the treatment assigned.

Primary endpoint OS analyses

OS in the ITT population was compared between the 2 treatment groups (ITT population) using the stratified log-rank test. One- and 2-sided p-values were presented. The study would be declared to have met its primary objective if the 1-sided p-value was less than 0.0215. The estimate of the HR and corresponding 95% CI were provided using a Cox proportional hazards (CPH) model including treatment and the 3 stratifications factors in the model. Survival for each arm was summarized using Kaplan Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates. The stratification factors were populated as per the IXRS assignment.

Subgroup analyses were conducted for each of the stratification factors (as per IXRS) and additional subgroups were utilized for the supportive analysis of the primary and key secondary endpoint. Summary statistics, HR and associated 95% CI were presented for each subgroup. Only 2-sided p-value were calculated and presented in the tables by the subgroups.

Supportive analyses for OS, conducted in the ITT population (unless otherwise noted), included:

The unstratified log-rank test and a CPH model (only treatment effect included in the model);

1. Multivariate analysis using the CPH model, including the 3 stratification factors and potential prognostic/predictive factors: age (<65, ≥65 years), race (white, Asian, other), gender, number of prior regimens (2, 3+), prior therapy, previous gastrectomy, GEJ involvement, presence of peritoneal metastases, presence of liver metastases, number of metastatic sites (1-2, 3+), measurable disease, histology subtype (diffuse, intestinal), and HER2 status;

   Factors included in the model were assessed for co-linearity and a stepwise selection process was applied to identify a final subset of prognostic/predictive factors in the model. Once the subset was established, treatment was added to the final model to assess its effect in the presence of the identified covariates;

   An exploratory analysis of treatment by factor interactions using the CPH model was conducted, using the factors identified in the final model above;

2. Subgroup analyses were also conducted for each of the stratification factors and the potential prognostic/predictive factors identified above. The HR and associated 95% CI were presented for each subgroup;

3. The primary efficacy analysis, as outlined above, were also run excluding any patients who did not have documented refractory mGC, as defined above in inclusion criteria #2 and #3 in section *Study participants*;

4. Additional sensitivity analyses defined in the statistical analysis plan (SAP):

   - The primary efficacy analysis that excluded/adjusted for all major protocol violations;
   - Stratified test analysis using the CRF designation instead of IVRS, assuming there are differences;
   - OS analysis using as-treated (AT) population;
   - Analysis described above in Section 10.4.1 was also run excluding high accrual (>25 patients) sites;
   - Analysis described above was also run using date of all collected events (death) and survival status as of 30-April-2018.

One IA for efficacy and futility was planned for the study after approximately half of the total target events were observed (192 deaths). The Lan-DeMets alpha-spending approach was used with O'Brien-Fleming stopping boundaries to guide the efficacy evaluation at the interim and final OS analysis. This approach accounted for multiple testing and preserved the overall 1-sided study significance level of 0.025. A fixed HR boundary was used to assess futility (non-binding). Stop due to futility would have been recommended if observed HR would have been ≥0.95 when conditional power would have been less than 2%. Stopping the study for efficacy would have been recommended if calculated 1-sided p-value would have been less than 0.0015. The corresponding HR for such significant results would have been less than approximately 0.63, associated with a mOS improvement from 5 to 7.9 months. The exact boundaries were derived based on the actual number of events used for the IA.

For the final analysis of the primary efficacy endpoint the result was considered as significant if 1-sided p-value was less than 0.0245 (this was subject to change based on the information/number of events at the IA). The corresponding HR for such significant result was less than approximately 0.808 associated with a mOS improvement from 5 to 8 months).

Key secondary endpoint PFS analyses

Since *PFS* was the only key secondary endpoint for regulatory registration purposes, no further multiplicity adjustments were made. Assuming that OS demonstrated significance at the 1-sided 0.025 level, PFS could subsequently be tested at the 2-sided 0.05 level.

PFS analyses largely followed the methodology specified above for OS. In line with FDA guidance additional sensitivity analyses were conducted on the ITT population. Subgroup analysis followed the logic applied to the primary endpoint investigation. The list of other planned examinations reads as follows:

- Analysis that included clinical progression as a PFS event in addition to the presence of radiological evidence of progression.
- Analysis including clinical progression as a PFS event that also counted initiation of non-study antitumor therapy as an event date rather than as date used to censor subsequent response assessment.
- Analysis that included all deaths and response assessments (without censoring missed visits) and counted as an event any one of the following list: radiological evidence of progression, clinical progression, initiation of non-study antitumor therapy, and death through the date of cut-off for survival.
- Analysis described above was also run excluding high accrual (>25 patients) sites.
- Analysis of time to first, second and third radiological tumour assessments from the date of randomization (Kaplan-Meier curves of times was depicted and the corresponding supporting tables were created; log-rank test were applied for examination and comparison of the two groups).

The PFS censoring rules are shown below in Table 4.

Table 4. PFS censoring rules

Situation	End Date	Censored	Assignment in PFS table
Documented radiological PD	Date of the first assessment of the series of the tests that determined PD	No	
Death during the study before PD	Date of death	No	
Treatment discontinuation for other than radiologic PD or death with no post-baseline tumor assessments	Date of randomization	Yes	Discontinued Follow Up
Treatment discontinuation for other than radiologic PD or death with post-baseline tumor assessments	Date of last adequate tumor assessment prior to initiation of non-study anti-tumor treatment	Yes	Discontinued Follow Up
Subjects still followed without radiologic PD as of cut-off date	Date of last adequate tumor assessment prior to cut-off date	Yes	Ongoing
Non-study anti-tumor treatment initiated before radiologic PD	Date of last adequate tumor assessment prior to initiation of non-study anti-tumor treatment	Yes	Initiated anti-tumor therapy
Non-study anti-tumor treatment initiated on date of radiologic PD	Date of radiologic PD (= date of initiation of non-study anti-tumor treatment)	No	
Death or radiologic PD after a missed tumor assessment	Date of last adequate tumor assessment prior to missed tumor assessment	Yes	Missed Visit
Death or radiologic PD after 91 days period since first dose (no post-baseline tumor assessments during this period)	Date of randomization	Yes	Missed Visit
Only NE tumor assessments after CR, PR, or SD	Date of last adequate tumor assessment prior to NE tumor assessments	Yes	Missed Visit
Ongoing patients with no post-baseline tumor	Date of randomization	Yes	Ongoing
assessments			
No baseline tumor assessment	Date of randomization	Yes	Depends on the discontinuation status and post-baseline tumor scan status – anyone of the 4 categories can take place

Other secondary efficacy endpoint analyses

All other secondary endpoints comparisons were made at the 2-sided 0.05 significance level.

The treatment comparison for *ORR* and *DCR* were based on the TR population using Fisher's exact test. Treatment estimates and differences were presented along with the associated 95% CIs.

The *time to deterioration of ECOG PS* to a score ≥2 was analysed using methodology described above for OS. A sensitivity analysis was performed using only on therapy ECOG assessments for analysis, i.e. excluding deaths during the survival follow-up period (when ECOG was not measured).

The *time to deterioration of QoL* by ≥5 points in global health status was assessed using the EORTC QLQ-C30 and QLQ-STO22. Scales was scored according to the EORTC scoring manual. Descriptive statistics, for both scales, for the summary scores, as well as the subscale scores were provided for each assessed time point. In addition, change in QoL scores at representative time points (i.e. prior to cycle 2,3, and 4) were determined for the summary, all domains and single items by subtracting each patient's score from their corresponding baseline score. In addition, time to QoL deterioration was evaluated for each arm using Kaplan-Meier estimates and compared using the log-rank test (and Cox proportional hazards models adjusting for the baseline value of the EORTC QLQ-C30 and QLQ-STO22 score, country and primary tumour type). Patients with no deterioration in EORTC QLQ-C30 and QLQ-STO22 scores were censored at the end of study, cut-off date or death date. A sensitivity analysis was similar to the aforementioned main analysis, but it was conducted using a decrease of ≥10 points to define deterioration in QoL.

Changes in the planned analyses

The original statistical analysis plan (SAP) version 1.05 was approved on 06-Jul-2016. Prior to database lock (and all statistical analyses), the SAP was amended once; version 2.0 was issued on 27-Apr-2018. Substantial changes to the SAP are summarized below in Table 5.

Table 5. Summary of substantial changes to the statistical analysis plan

Section	Key Changes
Section 8.1	Reference date for age calculation was changed from randomization date to the date the informed consent was signed.
Sections 8.7, 8.8, and Appendix H	Definitions for cycle windows and handling of multiple assessments were further detailed and documented.
Section 8.9	Time-adjusted incidence rate calculations were revised from 1 year to 100 years.
Section 8.12	Creatinine clearance levels for the severe renal function impairment group were added to the definition.
Section 8.13	Imputation rules for partial birth dates, missing end of exposure dates, and start of antitumor therapy dates were added.
Section 9.2	Definitions of CSR reportable protocol deviations were added to the existing Major Protocol Deviations.
Section 9.5.1, 9.6.1	Details of how prior cancer medical history and prior anti-cancer therapies are summarized were updated.
Section 9.5	Medical history was summarized for the AT population instead of the ITT population.
Section 10.2	List of subgroups for the efficacy analyses (OS and PFS) was revised to remove primary tumor site subgroup and add prior immunotherapy subgroup (PD1/PDL1).
Section 10.4.2.3	Additional sensitivity analyses were added including one excluding high-accrual (> 25 patients) sites.
Section 11.2.1, 11.2.2, 11.6.4	Subgroups for the key safety analyses (treatment-emergent adverse events and clinical laboratory data) were defined and the list of treatment-emergent adverse event summaries was updated.
Section 12	The efficacy bound (p-value) for the final analyses was derived based on the actual event count used for the interim analysis.
Appendices	Appendices were added: • Appendix C: Progression-free survival censoring rules • Appendix D: Standard laboratory ranges were updated • Appendix G: Date for the clinical cut-off was established and rules for submission database were added. • Appendix H: Data Handling Guidance that further details data handling rules for safety endpoints.

Abbreviations: AT = as-treated (population); CSR = clinical study report; ITT = intent-to-treat (population); OS = overall survival; PFS = progression-free survival

Results

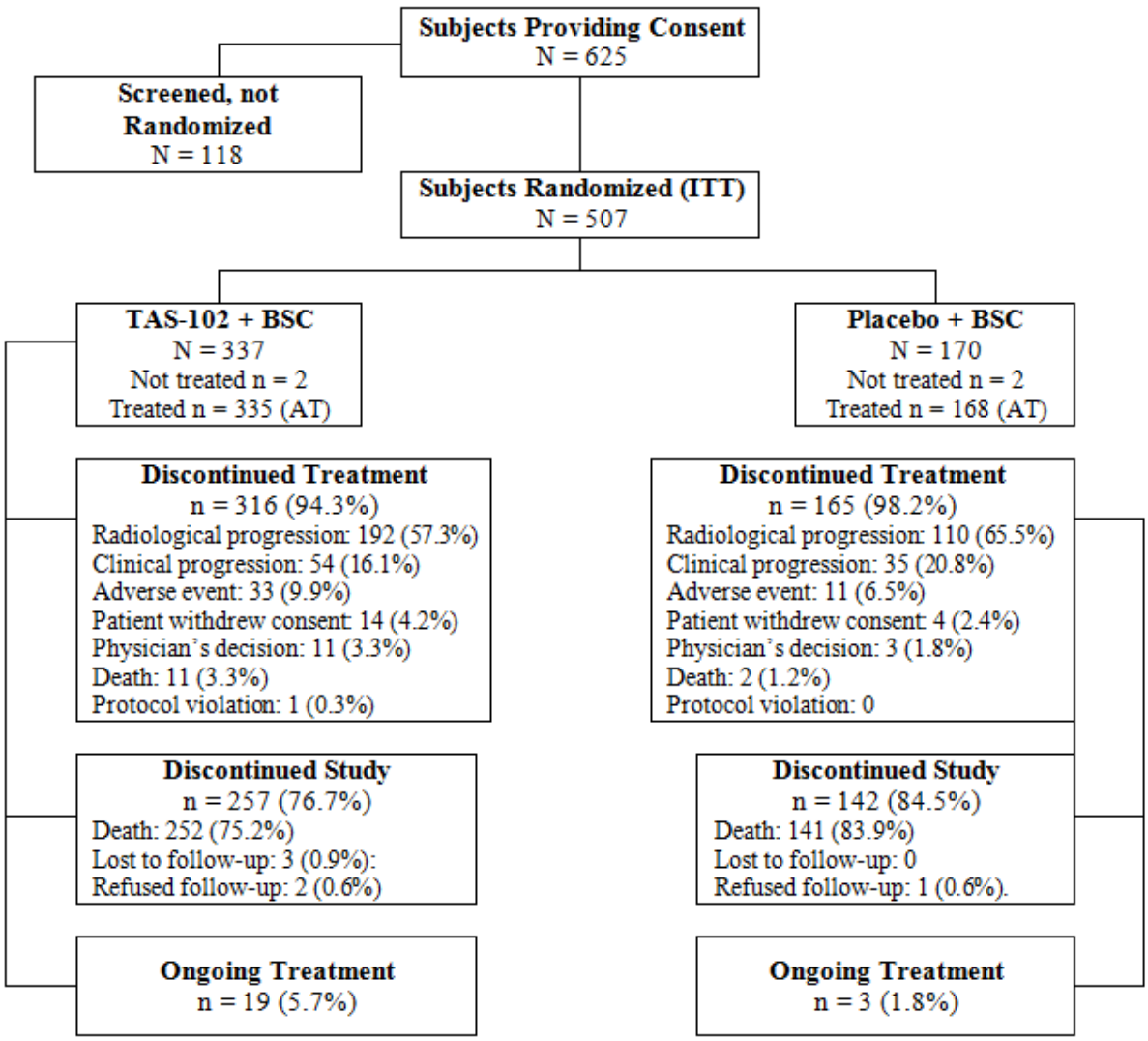
Recruitment and participant flow

Between 24-Feb-2016 and 05-Jan-2018, 507 patients were enrolled and randomly assigned (2:1) to the TAS-102 group (N=337) and the placebo group (N=170). The target number of events, i.e. 384 deaths, was reached on 27-Mar-2018, which is thus the OS data cut-off date. There occurred 11 additional deaths (TAS-102: 9; placebo: 2) in the time period between these two dates,. The cut-off date for all other (non-OS) clinical data was 31-Mar-2018. Median duration of survival follow-up was 10.7 months (TAS-102: 10.6 months; placebo: 10.7 months).

A total of 625 patients provided signed informed consent for participation in the study. Of these, 118 (18.9%) were screened but not randomized primarily (111/118 = 94%) due to screen failures. Of the 507 patients randomized (ITT population), 337 were assigned to TAS-102 and 170 were assigned to placebo.

Four patients (2 patients in each treatment group) did not receive study treatment. In the TAS-102 group, 1 patient died (before having received treatment) and 1 had a protocol violation; both patients in the placebo group withdrew consent (before having received treatment). The patient flow is depicted below in Figure 2 (alternatively see Figure 1 of Shitara, 2018).

Figure 2. Patient flow



Abbreviations: AT = as-treated (population); BSC = best supportive care; ITT = intent-to-treat (population)

Conduct of the study

Protocol amendments

The original study protocol was issued on 30-Jun-2015. Substantial changes to the protocol (including e.g. the addition of QoL to the [other] secondary endpoints) are described in order of issuance in Table 6.

Table 6. Summary of substantial changes in the protocol

Amendment No.	Date	Key Changes
Original	30 Jun 2015	Not applicable
Version 0.1 Rest of World	16 Jul 2015	Administrative; change in Medical Monitor
Version 1.0 Japan	10 Jul 2015	Added Appendix E: Supplemental Requirements for Japan Only Added Appendix F: Summary of Changes to Protocol
Version 1.1 Japan	16 Jul 2015	Administrative; change in Medical Monitor
Version 1.0 Rest of World Version 2.0 Japan	19 Feb 2016 22 Feb 2016	• Added Quality of Life to secondary endpoints • Revised footnote in the Study Schedule and throughout the document to clarify timing of screening period, randomization, and study treatment start. • Revised footnote in the Study Schedule to clarify timing of Eastern Cooperative Oncology Group (ECOG) performance status score collection. • Revised survival follow-up to exclude patients who have withdrawn consent from the study unless they request discontinuation of study treatment but agree to survival follow-up (this was not considered withdrawal of consent). • Revised inclusion/exclusion criteria definition of contraception to comply with Health Authority Request. Minor clarification was made to inclusion criterion #3d to allow patients who received postoperative adjuvant chemotherapy or chemoradiotherapy to continue the adjuvant therapy. • Clarified resumption criteria for patients with decreases in neutrophils. • Clarified Quality of Life assessments were to be performed prior to dose administration in each cycle. Clarified reference points of Quality of Life assessments from Weeks to Cycles. • Added definition of serious adverse reaction, and reporting requirements for serious adverse events, serious adverse reactions and suspected unexpected serious adverse reactions (SUSARs) per Health Authority request. • Clarified reporting requirements for medication errors and SUSARs.
Version 1.0 Germany	22 Feb 2016	The same changes were made as for Version 1.0 Rest of World amendment. **In addition** the following change was made: • Added new assessment: 12-lead electrocardiogram (ECG) was to be performed within 28 days prior to randomization.
Version 2.0 Rest of World Version 2.0 Germany Version 3.0 Japan	05 May 2016	• Clarified that steroids at doses ≤ 20 mg of prednisone equivalent per day for ≤ 2 weeks are permitted during the study. • Added dose interruption/resumption guidelines for febrile neutropenia per Health Authority Request. • Revised terminology pertaining to related adverse events: "related" was changed to "reasonably possible" and "not related" was changed to "not reasonably possible."
Version 4.0 Japan	23 Apr 2018	Appendix E: Supplemental requirements for Japan Only • The study period was changed from Jun 2018 to Dec 2018 to extend the planned study duration.

Protocol deviations

A CSR reportable protocol deviation was related to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessments that impact the safety of the patients or jeopardize the quality of the study data. In addition, among all CSR reportable protocol deviations, a set of "major protocol deviations" was defined as a means to measure adherence to key aspects of the protocol using pre-specified sensitivity analyses.

The occurrence of any *major protocol deviation* was similar between the treatment arms (TAS-102: 2.7%; placebo: 2.4%), see Table 7. The patient in the placebo arm who had received "Other concurrent chemotherapy … while receiving study treatment" had received ramucirumab.

Overall, 60 (17.8%) patients in the TAS-102 group and 14 (8.2%) patients in the placebo group had CSR reportable *(non-major) deviations*. Thirty-nine patients (11.6%) in the TAS-102 treatment group and 4 patients (2.4%) in the placebo group received the wrong treatment or incorrect dose, thus 43 patients overall. Of note, "wrong treatment" did not mean that a patient received TAS-102 instead of placebo or the other way round. Of these 43 patients, in 31 patients (in 2 of whom the event occurred twice), the dose of study medication was not held even though the ANC was below 1.5 x 10^9/L prior to dosing. In 6 patients (in one of whom it occurred 4 times), the patient took the wrong dose. In 4 patients, the height or weight was recorded incorrectly leading to a wrong BSA calculation. In 2 patients the wrong kit was given and in 2 patients the kits were not returned. Of note, for 2 patients, more than 1 reason than the RD3 category was assessed.

Table 7. Summary of protocol deviations

	Number (%) of Patients		
Deviation	**TAS-102 (N=337) n (%)**	**Placebo (N=170) n (%)**	**Total (N=507) n (%)**
Major CSR Reportable Deviations			
Any criteria	9 (2.7)	4 (2.4)	13 (2.6)
MRD1 – No histological confirmation of gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction	0	0	0
MRD2 – No metastatic disease	0	0	0
MRD3 – No measurable or non-measurable disease per RECIST v1.1	0	0	0
MRD4 – Received fewer than 2 prior regimens	7 (2.1)	1 (0.6)	8 (1.6)
MRD5 – Prior anticancer therapy within 3 weeks prior to study treatment administration	2 (0.6)	2 (1.2)	4 (0.8)
MRD6 – Previously received TAS-102	0	0	0
MRD7 – Received incorrect treatment (ie, randomized to 1 arm but received the other treatment)	0	0	0
MRD8 – Other concurrent chemotherapy or radiotherapy administered while receiving study treatment	0	1 (0.6)	1 (0.2)
CSR Reportable Deviations			
Any criteria	60 (17.8)	14 (8.2)	74 (14.6)
RD1 – Did not meet entry criteria	13 (3.9)	6 (3.5)	19 (3.7)
RD2 – Developed withdrawal criteria but were not withdrawn	4 (1.2)	1 (0.6)	5 (1.0)
RD3 – Received the wrong treatment or incorrect dose	39 (11.6)	4 (2.4)	43 (8.5)
RD4 – Received an excluded medication	2 (0.6)	1 (0.6)	3 (0.6)
RD5 – Critical ICF, GCP and other protocol deviations	6 (1.8)	2 (1.2)	8 (1.6)

Abbreviations: CSR = clinical study report; GCP = Good Clinical Practice; ICF = Informed Consent Form; MRD = major reportable deviation; RD = reportable deviation; RECIST = Response Evaluation Criteria in Solid Tumours

Baseline data

The demographic and other baseline characteristics for the ITT population are shown below in Table 8.

Table 8. Demographic and other baseline characteristics (ITT population)

Parameter	TAS-102 (N=337)	Placebo (N=170)	Total (N=507)
Gender, n (%)			
Male	252 (74.8%)	117 (68.8%)	369 (72.8%)
Female	85 (25.2%)	53 (31.2%)	138 (27.2%)
Age (years)			
Mean (SD)	62.8 (10.78)	62.0 (10.04)	62.5 (10.53)
Median	64.0	62.5	63.0
Min, Max	24, 89	32, 82	24, 89
Age group (years), n (%)			
< 65	183 (54.3%)	96 (56.5%)	279 (55.0%)
≥ 65	154 (45.7%)	74 (43.5%)	228 (45.0%)
≥ 65 - <75	103 (30.6%)	56 (32.9%)	159 (31.4%)
≥ 75	51 (15.1%)	18 (10.6%)	69 (13.6%)
Race, n (%)			
White	244 (72.4%)	113 (66.5%)	357 (70.4%)
Black or African American	1 (0.3%)	2 (1.2%)	3 (0.6%)
Asian	51 (15.1%)	29 (17.1%)	80 (15.8%)
Not Collectable	38 (11.3%)	24 (14.1%)	62 (12.2%)
Other	3 (0.9%)	2 (1.2%)	5 (1.0%)
Body Surface Area (m^2)			
Mean (SD)	1.747 (0.2131)	1.754 (0.1998)	1.749 (0.2086)
Median	1.750	1.740	1.740
Min, Max	1.20, 2.37	1.29, 2.52	1.20, 2.52
ECOG Performance Status, n (%)			
0	123 (36.5%)	68 (40.0%)	191 (37.7%)
1	214 (63.5%)	102 (60.0%)	316 (62.3%)
Region 1, n (%)			
Japan	46 (13.6%)	27 (15.9%)	73 (14.4%)
ROW1	291 (86.4%)	143 (84.1%)	434 (85.6%)
Region 2, n (%)			
Europe - EU[a]	180 (53.4%)	97 (57.1%)	277 (54.6%)
ROW2	157 (46.6%)	73 (42.9%)	230 (45.4%)
Region 3, n (%)			
USA	21 (6.2%)	5 (2.9%)	26 (5.1%)
ROW3	316 (93.8%)	165 (97.1%)	481 (94.9%)
Baseline Renal function, n (%) [b]			
Normal (CLcr >= 90 mL/min)	134 (39.8%)	68 (40.0%)	202 (39.8%)
Mild Impairment (CLcr 60-89 mL/min)	141 (41.8%)	71 (41.8%)	212 (41.8%)
Moderate Impairment (CLcr 30-59 mL/min)	58 (17.2%)	28 (16.5%)	86 (17.0%)
Severe Impairment (CLcr <30 mL/min)	2 (0.6%)	1 (0.6%)	3 (0.6%)
Missing	2 (0.6%)	2 (1.2%)	4 (0.8%)

Abbreviations: CrCl = creatinine clearance; ECOG = European Cooperative Oncology Group;
a Europe - EU refers to countries members of the European Union.
b CrCl based on Cockcroft-Gault using baseline creatinine.

The baseline disease characteristics for the ITT population are shown below in Table 9.

Table 9. Baseline disease characteristics (ITT population)

	TAS-102 (N=337)	Placebo (N=170)	Total (N=507)
Primary cancer type			
Gastric, n (%)	239 (70.9)	121 (71.2)	360 (71.0)
Gastroesophageal junction, n (%)	98 (29.1)	47 (27.6)	145 (28.6)
Both, n (%)	0	2 (1.2)	2 (0.4)
Tumor grade			
Well differentiated, n (%)	32 (9.5)	14 (8.2)	46 (9.1)
Moderately differentiated, n (%)	109 (32.3)	45 (26.5)	154 (30.4)
Poorly differentiated, n (%)	113 (33.5)	72 (42.4)	185 (36.5)
Unknown or missing, n (%)	83 (24.6)	39 (22.9)	122 (24.1)
Histology subtype			
Intestinal, n (%)	103 (30.6)	52 (30.6)	155 (30.6)
Diffused, n (%)	53 (15.7)	21 (12.4)	74 (14.6)
Mixed, n (%)	14 (4.2)	8 (4.7)	22 (4.3)
Unknown, n (%)	132 (39.2)	69 (40.6)	201 (39.6)
Not applicable, n (%)	35 (10.4)	20 (11.8)	55 (10.8)
Time from initial diagnosis to randomization (months)			
Mean (standard deviation)	26.98 (24.812)	25.63 (20.832)	26.53 (23.541)
Median	20.90	20.00	20.70
Min, max	3.6, 302.5	4.0, 190.4	3.6, 302.5
Time from confirmed metastasis to randomization (months)			
Mean (standard deviation)	19.44 (13.122)	19.12 (17.575)	19.33 (14.749)
Median	16.30	14.65	15.80
Min, max	0.6, 87.7	2.6, 189.7	0.6, 189.7
Had measurable disease, n (%)	**306 (90.8)**	**150 (88.2)**	**456 (89.9)**
Number of metastatic sites			
1-2, n (%)	155 (46.0)	72 (42.4)	227 (44.8)
3 or more, n (%)	182 (54.0)	98 (57.6)	280 (55.2)
Presence of liver metastases	**195 (57.9)**	**89 (52.4)**	**284 (56.0)**
Presence of lung metastases	**108 (32.0)**	**44 (25.9)**	**152 (30.0)**
Presence of peritoneal metastases	**87 (25.8)**	**53 (31.2)**	**140 (27.6)**
HER 2 status			
Positive, n (%)	67 (19.9)	27 (15.9)	94 (18.5)
Negative, n (%)	207 (61.4)	106 (62.4)	313 (61.7)
Not done, n (%)	62 (18.4)	37 (21.8)	99 (19.5)

Abbreviations: HER 2 = human epidermal growth factor receptor 2

Prior anti-cancer treatment

Prior anti-cancer treatment for the ITT population is shown below in Table 10.

Table 10 Prior anti-cancer treatment (ITT population)

	TAS-102 (N=337)	Placebo (N=170)	Total (N=507)
Had prior surgery related to gastric cancer, n (%)	**271 (80.4)**	**133 (78.2)**	**404 (79.7)**
Had previous gastrectomy, n (%)	**147 (43.6)**	**74 (43.5)**	**221 (43.6)**
Type of surgery related to gastric cancer			
Biopsy, n (%)	191 (56.7)	100 (58.8)	291 (57.4)
Resection of primary lesion, n (%)	136 (40.4)	63 (37.1)	199 (39.3)
Other, n (%)	75 (22.3)	35 (20.6)	110 (21.7)
Had prior radiotherapy related to gastric cancer, n (%)	**71 (21.1)**	**26 (15.3)**	**97 (19.1)**
Number of prior treatment regimens, n (%)			
2	126 (37.4)	64 (37.6)	190 (37.5)
3	134 (39.8)	60 (35.3)	194 (38.3)
4 or more	77 (22.8)	46 (27.1)	123 (24.3)
Prior systemic therapeutic agents[a,b], n (%):			
Fluoropyrimidine[c]	336 (99.7)	170 (100)	506 (99.8)
Platinum[d]	337 (100)	170 (100)	507 (100)
Taxane[e]	311 (92.3)	148 (87.1)	459 (90.5)
Ramucirumab[f]	114 (33.8)	55 (32.4)	169 (33.3)
Irinotecan[g]	183 (54.3)	98 (57.6)	281 (55.4)
HER2i[h]	60 (17.8)	24 (14.1)	84 (16.6)
Immunotherapy (PD1/PDL1)[i]	25 (7.4)	7 (4.1)	32 (6.3)
Other	77 (22.8)	41 (24.1)	118 (23.3)
Intent of prior systemic cancer therapy[a], n (%)			
Neoadjuvant	37 (11.0)	15 (8.8)	52 (10.3)
Adjuvant	56 (16.6)	35 (20.6)	91 (17.9)
Advanced/metastatic	337 (100.0)	170 (100.0)	507 (100.0)
[illegible]	[illegible]	[illegible]	[illegible]

Abbreviations: HER 2 = human epidermal growth factor receptor 2; PD = programmed cell death (receptor)

[a] Patients with multiple levels were counted in each applicable category.
[b] Includes all prior systemic therapies (neoadjuvant, adjuvant, metastatic).
[c] Fluoropyrimidine includes 5-FU (fluorouracil), capecitabine, doxifluridine, S-1, tegafur, tegafur-uracil (UFT), and additional agents that were collected as 'Other' and later re-mapped to fluoropyrimidine.
[d] Platinum includes oxaliplatin, cisplation, carboplatin, and additional agents that were collected as 'Other' and later remapped to platinum.
[e] Taxane includes docetaxel, paclitaxel, nab-paclitaxel (abraxane), and additional agents that were collected as 'Other' and later remapped to taxane.
[f] Ramucirumab as monotherapy or in combination with other agent(s).
[g] Irinotecan includes irinotecan and CPT-11 and additional agents that were collected as 'Other' and later remapped to irinotecan.
[h] HER2i includes trastuzumab, pertuzumab and TDM-1.
[i] Immunotherapy includes all PD1/PDL1 agents.

See Table 11 for the number of prior regimens and the therapeutic agents that were given for metastatic disease only.

Table 11. Prior anti-cancer treatment for metastatic disease (ITT population)

Parameter	TAS-102 (N=337)	Placebo (N=170)	Total (N=507)
Number of Prior Regimens for Metastatic Cancer n (%)			
1	13 (3.9)	2 (1.2)	15 (3.0)
2	151 (44.8)	81 (47.6)	232 (45.8)
3	120 (35.6)	62 (36.5)	182 (35.9)
≥4	53 (15.7)	25 (14.7)	78 (15.4)
Prior Systemic Cancer Therapeutic Agents to Treat Metastatic Cancer [1] , n (%)			
Yes	337 (100.0)	170 (100.0)	507 (100.0)
Fluoropyrimidine [3]	327 (97.0)	163 (95.9)	490 (96.6)
Platinum [4]	317 (94.1)	160 (94.1)	477 (94.1)
Taxane [5]	306 (90.8)	146 (85.9)	452 (89.2)
Irinotecan [6]	183 (54.3)	98 (57.6)	281 (55.4)
HER2i [8]	59 (17.5)	23 (13.5)	82 (16.2)
Immunotherapy (PD1/PDL1) [7]	25 (7.4)	7 (4.1)	32 (6.3)
Other	76 (22.6)	38 (22.4)	114 (22.5)

[1] Patients with multiple levels are counted in each applicable category. [2] Includes all prior systemic therapies (Neoadjuvant, Adjuvant, Metastatic).
[3] Fluoropyrimidine includes 5-FU (Fluorouracil), Capecitabine, Doxifluridine, S-1, Tegafur and UFT and some agents that were collected as 'Other' and re-mapped later to Fluoropyrimidine.
[4] Platinum includes Oxaliplatin, Cisplation, Carboplatin and some agents that were collected as 'Other' and re-mapped later to Platinum.
[5] Taxane includes Docetaxel, Paxlitaxel, Nub-Paclitaxel (abraxane), and same agents that were collected as =Other| and re-mapped later to Taxane.
[6] Irinotecan includes Irinotecan and CPT-11, and same agents that were collected as =Other| and re-mapped later to Irinotecan.
[7] Immunotherapy includes all PD1/PDL1 agents. [8] HER2i includes Trastuzumab, Pertuzumab and TDM-1. Data Source: ADSL, ADCM

All patients in both treatment arms had received ≥2 prior systemic treatment regimens. The percentage of patients that had received ≥2 prior treatment regimens for metastatic disease was 96.1% in the TAS-102 arm vs. 98.8% in the placebo arm. The median number of prior treatment regimens for metastatic disease was 3 (range 1-9) vs. 3 (range 1-5), respectively. Nearly all patients in both circumstances had received prior fluoropyrimidine and prior platinum, and approximately 90% had received prior taxane therapy. Over half of patients (in both circumstances) had received prior irinotecan.

The most frequently reported most recent regimens prior to randomization for the ITT population were taxane (48.7%), fluoropyrimidine (32.3%), irinotecan (32.9%), and platinum (20.3%). Most patients were refractory to their last regimen prior to randomization, i.e. 85.4% - 98.2% across these regimens.

Prior and concomitant other medication

Other prior medication use was reported by 85.1% of patients in the TAS-102 group and 86.9% in the placebo group. The most frequently reported prior medications (≥20%) were in the WHO ATC Level III categories of drugs for peptic ulcer and gastroesophageal reflux disease (49.3%), opioids (25.2%), and antithrombotic agents (21.1%).

Concomitant medication use was reported by 90.1% of patients in the TAS-102 group and 84.5% in the placebo group. The most frequently reported concomitant medications (≥20%) were in the WHO ATC Level III categories of opioids (31.0%), drugs for peptic ulcer and gastroesophageal reflux disease (28.8%), other analgesics and antipyretics (21.1%), and propulsives (20.1%)

The use of any supportive blood product and/or growth factor was reported for 30.7% of patients in the TAS-102 and 7.1% in the placebo group. In the TAS-102 and placebo groups, respectively, supportive products for neutropenia were reported for 17.3% and 1.8% of patients, supportive products for thrombocytopenia were reported for 0.9% and 0%, and supportive products for anaemia were reported for 18.2% and 5.4%.

Post-discontinuation anti-cancer treatment

Per protocol, there was no unblinding at the time of disease progression. The use of post-discontinuation anti-cancer therapy (PDT) was not specified per protocol. PDT for the ITT population is shown below in Table 12. PDT included amongst others ramucirumab, immunotherapy (including nivolumab), irinotecan, and paclitaxel. The proportion of patients receiving systemic PDT was similar between arms (24.6% vs. 26.5%), as were the proportions of patients for whom PDT included ramucirumab (3.3% vs. 2.4%) or immunotherapy (4.5% vs. 4.7%).

Table 12. Post-discontinuation anti-cancer treatment (ITT population)

Treatment, n (%)	**TAS-102 N = 337**	**Placebo N = 170**
Surgery	47 (13.9)	28 (16.5)
Radiotherapy	8 (2.4)	5 (2.9)
Any systemic Therapy	83 (24.6)	45 (26.5)
Number of regimens:		
1	53 (15.7)	25 (14.7)
2	16 (4.7)	7 (4.1)
≥3	14 (4.2)	13 (7.6)
Any regimen containing ramucirumab	11 (3.3)	4 (2.4)
Any regimen containing immunotherapy	15 (4.5)	8 (4.7)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

Numbers analysed

The analysis populations are shown below in Table 13. The ITT population, consisting of all randomized patients, was used for all primary and secondary analyses of efficacy except as otherwise specified.

Table 13. **Analysis populations**

	Number of patients/total number of patients randomized (%)		
Analysis population	**TAS-102**	**Placebo**	**Total**
Intent-to-treat (ITT)	337/337 (100)	170/170 (100)	507/507 (100)
As-treated (AT)	335/337 (99.4)	168/170 (98.8)	503/507 (99.2)
Tumour response (TR)	290/337 (86.1)	145/170 (85.3)	435/507 (85.8)

Outcomes and estimation

Primary endpoint (overall survival [OS])

Primary analysis

The planned interim analysis was performed at 220 death events (refer to section *Ancillary analysis* for results). Neither the efficacy nor futility boundaries were met for any of the analyses and the DMC recommended to continue the study until completion, per protocol.

Treatment with TAS-102 resulted in a statistically significant improvement in OS compared to placebo (Table 14 and Figure 3), with a HR of 0.69 (95% CI: 0.560, 0.855; 1-sided p=0.0003 (boundary for final analysis 1-sided alpha=0.0215); stratified log-rank test) corresponding to a 31% reduction in the risk of death in the TAS-102 group. The mOS was 5.7 months (95% CI: 4.8, 6.2) for the TAS-102 group vs. 3.6 months (95% CI: 3.1, 4.1) for the placebo group (Δ +2.1 months). The median duration of survival follow-up was 10.6 months for the TAS-102 group and 10.7 months for the placebo group.

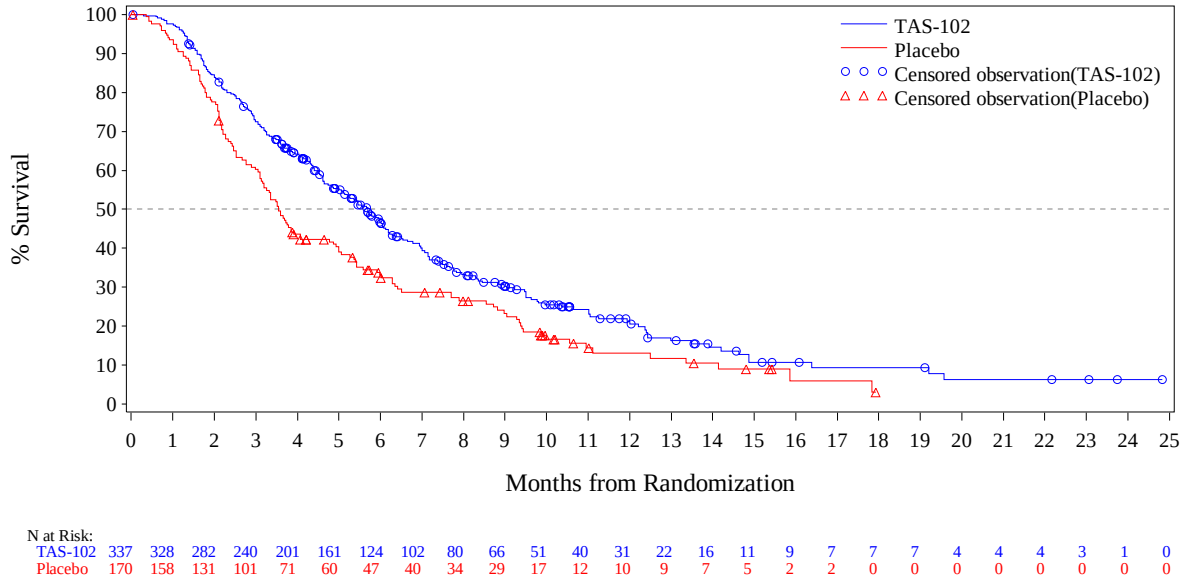
Table 14. Summary of overall survival endpoint (ITT population)

	TAS-102 N = 337	**Placebo N = 170**
Number of events (deaths), n (%)	244 (72.4)	140 (82.4)
Censored	93 (27.6)	30 (17.6)
Overall survival		
Median, months	5.7	3.6
95% CI, months	4.8, 6.2	3.1, 4.1
Hazard ratio	0.69 (0.560, 0.855)	
1-sided p-value[a]	0.0003	
2-sided p-value	0.0006	
Survival at 3 months, % (95% CI)	72.4 (67.3, 76.9]	60.3 (52.4, 67.2)
Survival at 6 months, % (95% CI)	46.7 (41.1, 52.2)	33.1 (25.9, 40.3)
Survival at 9 months, % (95% CI)	30.3 (24.9, 35.8)	23.3 (16.8, 30.3)
Survival at 12 months, % (95% CI)	21.2 (16.1, 26.7)	13.0 (7.7, 19.8)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

[a] boundary for final analysis 1-sided alpha = 0.0215

Figure 3. Kaplan-Meier curve of overall survival (ITT population)



Sensitivity analyses

The following **sensitivity analyses** were performed for OS:

- **Analysis 1:** Non-stratified log-rank test (that is, only treatment effect in the model) for the ITT population.
- **Analysis 2:** ITT population excluding patients not meeting inclusion criteria #2 or #3 (see section **Study participants** above).
- **Analysis 3:** ITT population excluding patients with major protocol deviations.
- **Analysis 4:** Based on CRF-designated stratification factors for the AT population.
- **Analysis 5:** By treatment group for the AT population.
- **Analysis 6:** Excluding sites with high accrual.
- **Analysis 7:** Using the date of all collected events (deaths) and survival status as of 30-Apr-2018.

An overview of the results of these analyses is provided below in Table 15.

Table 15. Sensitivity analyses of overall survival

Analysis	TAS-102		Placebo		HR (95% CI)	p-value[a]
	N	mOS (m)	N	mOS (m)		
Analysis 1	337	5.7	170	3.6	0.71 (0.580, 0.880)	0.0007
Analysis 2	333	5.7	169	3.6	0.70 (0.567, 0.867)	0.0005
Analysis 3	330	5.7	169	3.6	0.70 (0.566, 0.866)	0.0005
Analysis 4	335	5.7	168	3.6	0.68 (0.554, 0.847)	0.0002
Analysis 5	335	5.7	168	3.6	0.69 (0.560, 0.856)	0.0003
Analysis 6	304	5.7	149	3.4	0.60 (0.475, 0.748)	<0.0001
Analysis 7	337	5.6	170	3.6	0.71 (0.575, 0.873)	0.0006

Abbreviations: CI = confidence interval; HR = hazard ratio; m = months; mOS = median overall survival; N = number of patients in arm

[a] one-sided p-value

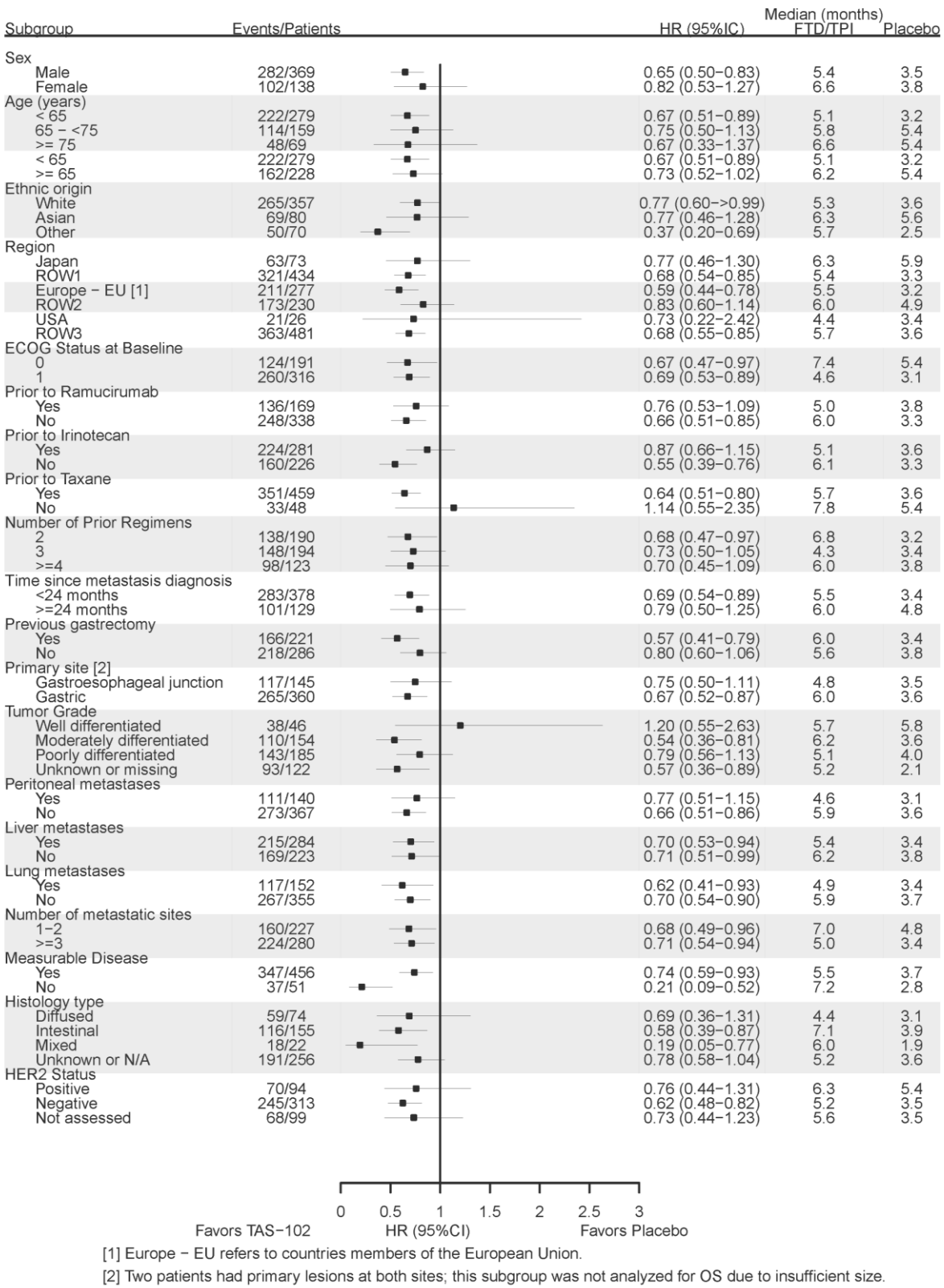
Multivariate analyses of potential prognostic factors for OS were performed. The factors included the stratification factors region, ECOG status at baseline, and prior treatment with ramucirumab, as well as age group (<65 vs. ≥65 years), race, gender, number of prior regimens, prior treatment with a taxane, prior treatment with irinotecan, previous gastrectomy, gastroesophageal junction involvement, metastatic site (peritoneal, liver, lung), number of metastatic sites, measurable disease, histology subtype, and HER2 status at baseline. Stepwise selection was performed to identify the final subset of prognostic/predictive factors: treatment, region, ECOG status at baseline, prior treatment with ramucirumab, age group (<65 vs. ≥65 years), number of prior regimens, number of metastatic sites, histology subtype, and HER2 status at baseline. In the resulting final Cox proportional hazard model, none of the listed factors were shown to modify the effect of treatment (all interaction p-values were >0.24). The multivariate model estimate for the HR for TAS-102 relative to placebo remained at 0.69 (95% CI: 0.560, 0.851; p = 0.0005), which is consistent with the primary (bivariate and stratified) analysis of OS.

Subgroup analyses

A forest plot summarizing the stratified subgroup analyses for OS in the ITT population is presented in Figure 1. The only subgroup analysis that is not included in this figure is the one for prior immunotherapy:

- Yes: events/patients = 18/25 vs. 6/7; HR=0.22 (95% CI: 0.06, 0.86); mOS 6.0 vs. 3.5 months.
- No: events/patients = 226/312 vs. 134/163; HR=0.71 (95% CI: 0.57, 0.88); mOS 5.7 vs. 3.6 months.

Figure 4. Forest plot summarizing subgroup analyses of overall survival (ITT population)



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; FTD/TPI = TAS-102; HER 2 = human epidermal growth factor receptor 2; HR = hazard ratio; ROW = rest of world; USA = United States of America

Secondary endpoints

Progression-free survival (PFS)

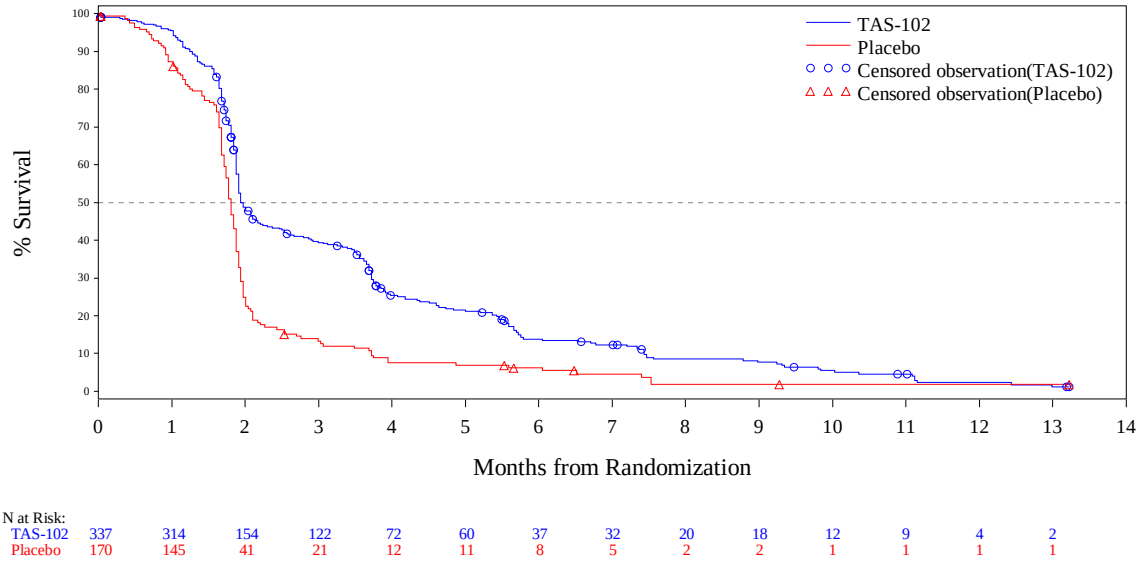
Treatment with TAS-102 resulted in a statistically significant improvement in PFS compared to placebo (Table 16 and Figure 5), with a HR of 0.57 (95% CI: 0.467, 0.701; p<0.0001 [2-sided]; stratified log-rank test), corresponding to a 43% reduction in the risk of disease progression in the TAS-102 group. The mPFS was 2.0 months (95% CI: 1.9, 2.3) for the TAS-102 group vs. 1.8 months (95% CI: 1.7, 1.9) for the placebo group (Δ +0.2 months).

Table 16. Summary of progression-free survival endpoint (ITT population)

	TAS-102 N = 337	**Placebo N = 170**
Number of events, n (%)		
Progression	209 (62.0)	113 (66.5)
Death	78 (23.1)	43 (25.3)
Censored	50 (14.8)	14 (8.2)
Discontinued follow-up	12 (3.6)	1 (0.6)
Initiated antitumor therapy	8 (2.4)	6 (3.5)
Missed visit (>91 days since last contact)	10 (3.0)	3 (1.8)
Follow-up ongoing	20 (5.9)	4 (2.4)
Progression-free survival		
Median, months	2.0	1.8
95% CI, months	1.9, 2.3	1.7, 1.9
Hazard ratio (95% CI)	0.57 (0.467, 0.701)	
2-sided p-value	<0.0001	
PFS at 2 months, % (95% CI)	49.7 (44.1, 55.1)	25.3 (18.9, 32.1)
PFS at 4 months, % (95% CI)	26.8 (21.9, 31.9)	7.7 (4.2, 12.5)
PFS at 6 months, % (95% CI)	14.6 (10.7, 19.0)	6.4 (3.2, 10.9)
PFS at 8 months, % (95% CI)	9.4 (6.2, 13.3)	2.8 (0.8, 6.8)

Abbreviations: ITT = intent-to-treat; CI = confidence interval; N = number of patients in arm; n = number of patients in group; PFS = progression-free survival

Figure 5. Kaplan-Meier curve of progression-free survival (ITT population)



The following **sensitivity analyses** were performed for PFS:

- **Analysis 1:** Including clinical progression as a progression event.
- **Analysis 2:** Including clinical progression and initiation of new antitumor therapy as progression events.
- **Analysis 3:** Including clinical progression, initiation of new antitumor therapy, and all deaths without censoring missed visits.
- **Analysis 4:** Excluding sites with high accrual.
- **Analysis 5:** Analysis of time to first, second and third radiological tumour assessments from the date of randomization.

An overview of the results of the first four of these analyses is provided below in Table 17. The results of **Analysis 5** are not shown, but these confirmed that the assessments were performed to schedule and that timing was similar among the two arms.

Table 17. Sensitivity analyses of progression-free survival

Analysis	TAS-102 arm		Control arm		HR (95% CI)	p-value[a]
	N	mPFS (m)	N	mPFS (m)		
Analysis 1	337	1.9	170	1.8	0.55 (0.452, 0.674)	<0.0001
Analysis 2	337	1.9	170	1.8	0.55 (0.454, 0.675)	<0.0001
Analysis 3	337	1.9	170	1.8	0.56 (0.460, 0.681)	<0.0001
Analysis 4	304	1.9	149	1.8	0.48 (0.382, 0.593)	<0.0001

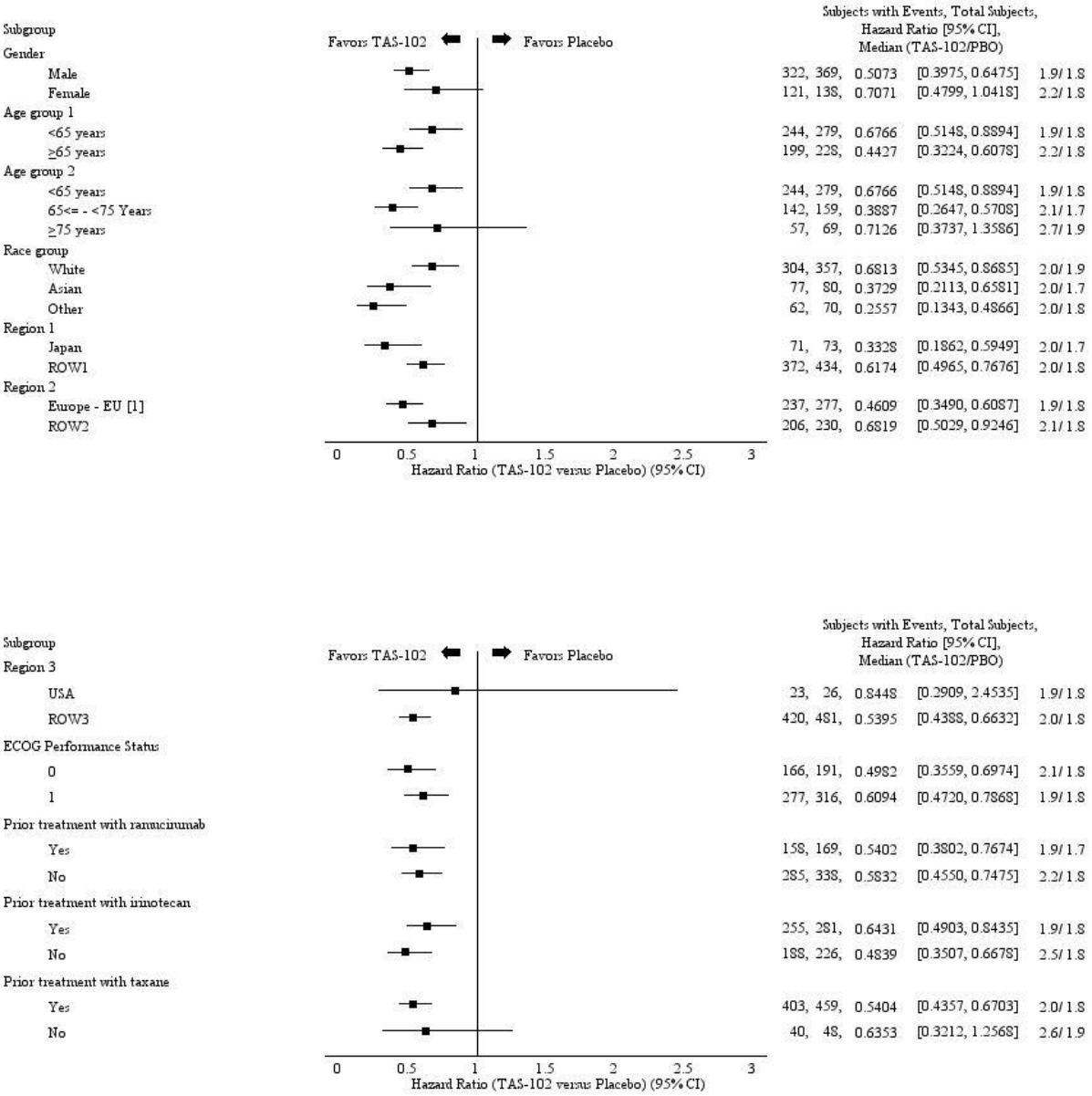
Abbreviations: CI = confidence interval; HR = hazard ratio; m = months; mPFS = median progression-free survival; N = number of patients in arm

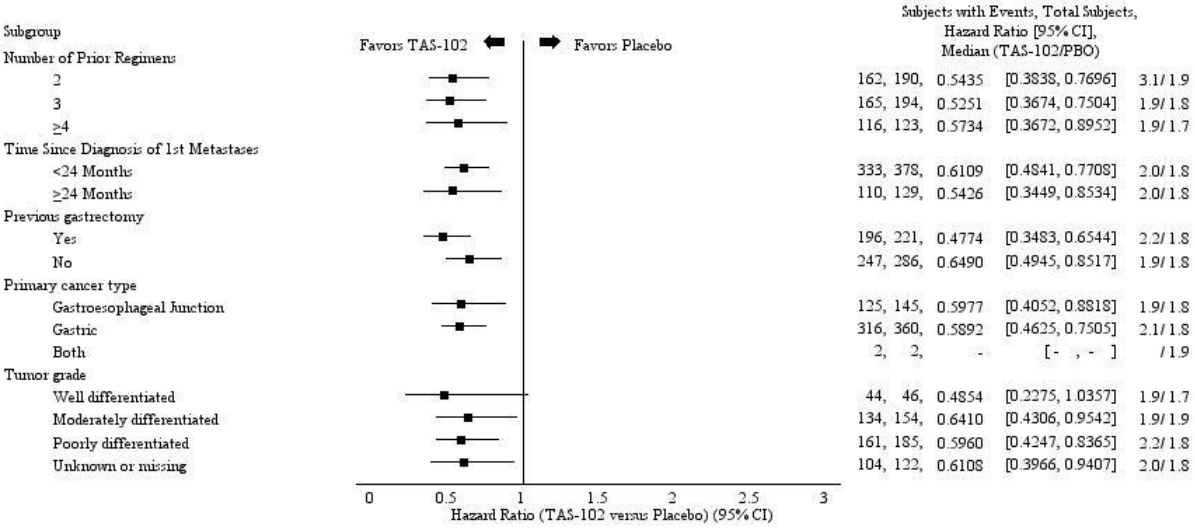
[a] two-sided p-value

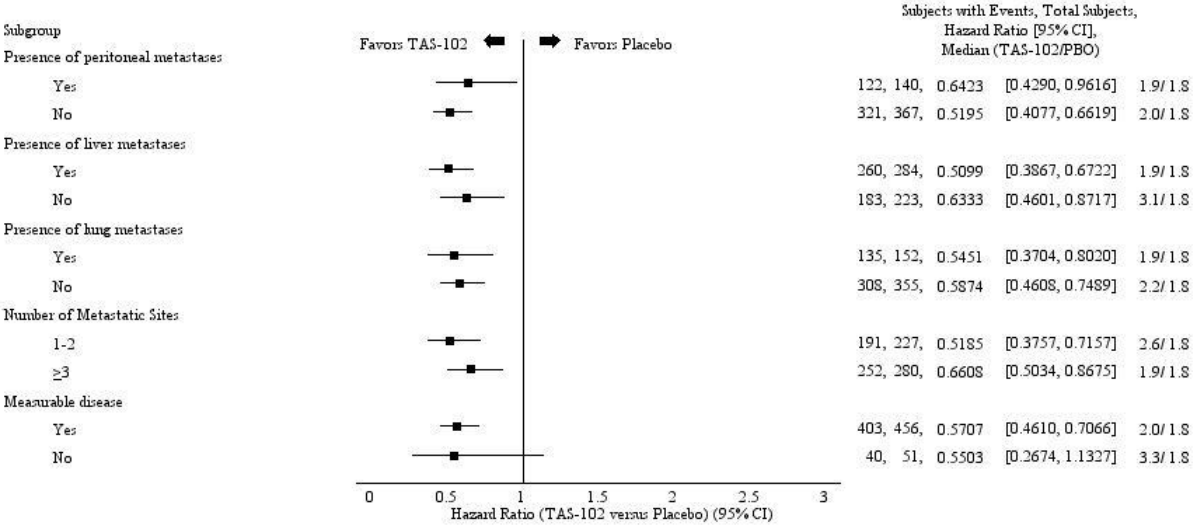
A forest plot summarizing the stratified subgroup analyses for PFS in the ITT population is presented in Figure 6 (alternatively see page 11 of Supplementary appendix of Shitara, 2018). Again, the only subgroup analysis that is not included in this figure is the one for prior immunotherapy:

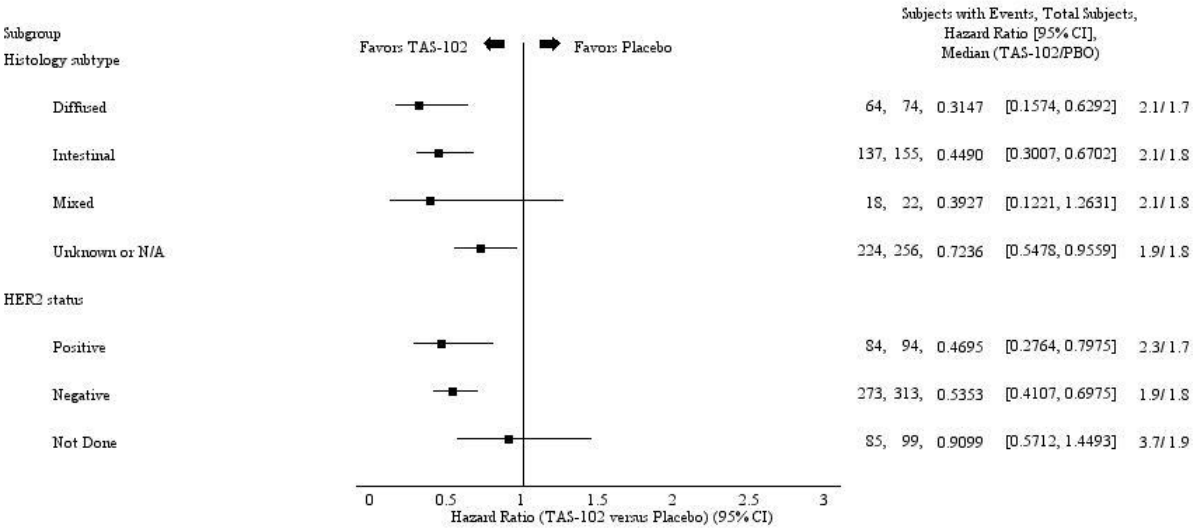
- Yes: events/patients = 22/25 vs. 7/7; HR= 0.4782 ((95% CI: 0.1413, 1.6184); mPFS 2.4 vs. 1.9 months.
- No: events/patients = 265/312 vs. 149/163 ; HR= 0.5774 (95% CI: 0.4690, 0.7110); mPFS 2.0 vs. 1.8 months.

Figure 6. Forest plot summarizing subgroup analyses of progression-free survival (ITT population)




Subgroup
Favors TAS-102
Favors Placebo
Subjects with Events, Total Subjects, Hazard Ratio [95% CI], Median (TAS-102/PBO)
Number of Prior Regimens
2 162, 190, 0.5435 [0.3838, 0.7696] 3.1/1.9
3 165, 194, 0.5251 [0.3674, 0.7504] 1.9/1.8
≥4 116, 123, 0.5734 [0.3672, 0.8952] 1.9/1.7
Time Since Diagnosis of 1st Metastases
<24 Months 333, 378, 0.6109 [0.4841, 0.7708] 2.0/1.8
≥24 Months 110, 129, 0.5426 [0.3449, 0.8534] 2.0/1.8
Previous gastrectomy
Yes 196, 221, 0.4774 [0.3483, 0.6544] 2.2/1.8
No 247, 286, 0.6490 [0.4945, 0.8517] 1.9/1.8
Primary cancer type
Gastroesophageal Junction 125, 145, 0.5977 [0.4052, 0.8818] 1.9/1.8
Gastric 316, 360, 0.5892 [0.4625, 0.7505] 2.1/1.8
Both 2, 2, - [- , -] /1.9
Tumor grade
Well differentiated 44, 46, 0.4854 [0.2275, 1.0357] 1.9/1.7
Moderately differentiated 134, 154, 0.6410 [0.4306, 0.9542] 1.9/1.9
Poorly differentiated 161, 185, 0.5960 [0.4247, 0.8365] 2.2/1.8
Unknown or missing 104, 122, 0.6108 [0.3966, 0.9407] 2.0/1.8
0 0.5 1 1.5 2 2.5 3
Hazard Ratio (TAS-102 versus Placebo) (95% CI)


Subgroup
Favors TAS-102
Favors Placebo
Subjects with Events, Total Subjects, Hazard Ratio [95% CI], Median (TAS-102/PBO)
Presence of peritoneal metastases
Yes 122, 140, 0.6423 [0.4290, 0.9616] 1.9/1.8
No 321, 367, 0.5195 [0.4077, 0.6619] 2.0/1.8
Presence of liver metastases
Yes 260, 284, 0.5099 [0.3867, 0.6722] 1.9/1.8
No 183, 223, 0.6333 [0.4601, 0.8717] 3.1/1.8
Presence of lung metastases
Yes 135, 152, 0.5451 [0.3704, 0.8020] 1.9/1.8
No 308, 355, 0.5874 [0.4608, 0.7489] 2.2/1.8
Number of Metastatic Sites
1-2 191, 227, 0.5185 [0.3757, 0.7157] 2.6/1.8
≥3 252, 280, 0.6608 [0.5034, 0.8675] 1.9/1.8
Measurable disease
Yes 403, 456, 0.5707 [0.4610, 0.7066] 2.0/1.8
No 40, 51, 0.5503 [0.2674, 1.1327] 3.3/1.8
0 0.5 1 1.5 2 2.5 3
Hazard Ratio (TAS-102 versus Placebo) (95% CI)



[1] Europe - EU refers to countries members of the European Union.

Tumour response (ORR and DCR)

As shown is Table 18, the **ORR** (CR + PR) was numerically higher for the TAS-102 arm when compared to the placebo arm (4.5% vs. 2.1%, respectively; Δ +2.4% [95% CI: -0.9, 5.7]; p=0.2833). The median duration of response (DoR) was 3.7 months for the 13 responders in the TAS-102 group vs. 3.8 months for the 3 responders in the placebo group (p=0.4506 [1-sided]).

A statistically significant improvement was observed in the **DCR** (CR + PR + SD) for the TAS-102 arm when compared to the placebo arm (44.1% vs. 14.5%, respectively; Δ +29.7% [95% CI: 21.6, 37.7], p<0.0001).

Table 18. Summary of tumour response (TR Population)

	TAS-102 N = 290	**Placebo N = 145**
Best overall response, n (%)		
Complete response (CR)	1 (0.3)	0
Partial response (PR)	12 (4.1)	3 (2.1)
Stable disease (SD)	115 (39.7)	18 (12.4)
Progressive disease (PD)	120 (41.4)	90 (62.1)
Not evaluable	42 (14.5)	34 (23.4)
Objective response rate, %	4.5	2.1
95% CI	2.4, 7.5	0.4, 5.9
p-value[c]	0.2833	
Disease control rate, %	44.1	14.5
95% CI	38.3, 50.1	9.2, 21.3
p-value[c]	<0.0001	

	TAS-102 N = 290	Placebo N = 145

Abbreviations: CI = confidence interval; N = number of patients in arm; n = number of patients in group; TR = tumour response

[c] Fisher's exact test (2-sided)

Time to deterioration to ECOG PS ≥2

In the ITT population, treatment with TAS-102 resulted in a statistically significant increase in the median time to deterioration to ECOG PS ≥2 compared to placebo (HR=0.69; 95% CI: 0.562, 0.854; p=0.0005 [2-sided]). The median time to deterioration to ECOG PS ≥2 was 4.3 months (95% CI: 3.7, 4.7) in the TAS-102 arm vs. 2.3 months (95% CI: 2.0, 2.8) in the placebo arm.

A sensitivity analysis was performed, using only on therapy ECOG assessments for analysis, i.e. excluding deaths during the survival follow-up period. For this analysis, 214/337 patients (63.5%) in the TAS-102 arm were censored and 90/170 patients (52.9%) in the placebo arm. The median time to ECOG PS ≥2 was 5.5 months in the TAS-102 arm (95% CI: 4.4, 6.9) vs. 2.2 months (95% CI: 1.9, 3.0) in the placebo arm (HR=0.54; 95% CI: 0.404, 0.721; p<0.0001 [2-sided]).

Time to deterioration of quality of life

Quality of life (**QoL**) was assessed using the EORTC QLQ-C30 and QLQ-STO22. Table 19 shows a summary of the absolute values and change from baseline in QoL scales for the ITT population. It can be seen that QoL was balanced at baseline, and that there were no (mean/median) changes ≥10 points in overall QoL from baseline up to cycle 3 in either treatment group. The number (and percentage) of patients completing the questionnaires decreased with each cycle, as the compliance (for the EORTC QLQ-C30 - global health status) was at cycle 1, 84.9% in the TAS-102 arm vs. 78.7% in the placebo arm, at cycle 2, 57.8% vs. 36%, and at cycle 3, 37.3% vs. 14%, respectively. Conversely, at cycle 3, in the TAS-102 arm 209/330 (63.3%) of EORTC QLQ-C30 - global health status values was missing vs. 140/163 (85.9%) in the placebo arm, and these percentages increased further thereafter.

Table 19. Summary of absolute values and change from baseline in QoL scales (ITT population)

Parameter Cycle/Day Statistics	TAS-102 (N=337) n (%)	Placebo (N=170) n (%)	Total (N=507) n (%)
QLQ-C30 - Global Health Status			
Baseline			
n	330	163	493
Mean (SD)	58.4 (20.23)	58.4 (19.72)	58.4 (20.04)
Median	58.3	58.3	58.3
Min, Max	0, 100	17, 100	0, 100
Cycle 1			
n	279	127	406
Mean (SD)	56.0 (20.67)	54.3 (23.54)	55.5 (21.59)
Median	58.3	50.0	50.0
Min, Max	0, 100	0, 100	0, 100
Cycle 1 Change from Baseline			
n	279	127	406
Mean (SD)	-2.7 (17.56)	-5.9 (22.20)	-3.7 (19.17)
Median	0.0	0.0	0.0
Min, Max	-100, 42	-67, 42	-100, 42
Cycle 2			
n	187	58	245
Mean (SD)	54.1 (21.16)	54.9 (21.06)	54.3 (21.09)
Median	50.0	50.0	50.0
Min, Max	0, 100	17, 100	0, 100
Cycle 2 Change from Baseline			
n	187	58	245
Mean (SD)	-5.9 (20.51)	-7.3 (25.80)	-6.3 (21.83)
Median	0.0	0.0	0.0
Min, Max	-83, 58	-83, 50	-83, 58
Cycle 3			
n	121	23	144
Mean (SD)	57.1 (20.74)	59.8 (18.74)	57.5 (20.40)
Median	50.0	66.7	58.3
Min, Max	0, 100	17, 100	0, 100
Cycle 3 Change from Baseline			
n	121	23	144
Mean (SD)	-4.1 (18.26)	-1.4 (22.00)	-3.6 (18.85)
Median	0.0	0.0	0.0
Min, Max	-67, 58	-50, 42	-67, 58

No statistically significant differences in the **time to deterioration of QoL** scores between TAS-102 and placebo groups were observed. Treatment with TAS-102 resulted in a numerically longer median time to deterioration by ≥5 points in global health status using the QoL questionnaires compared to placebo. The median time to deterioration was 2.6 months (95% CI: 2.3, 3.3) in the TAS-102 arm (N=288 for this analysis) vs. 2.3 months (95% CI: 1.4, not available [NA]) in the placebo arm (N=130) (HR=1.27; 95% CI: 0.854, 1.875; p=0.2350 [2-sided]). A sensitivity analysis using a decrease of ≥10 (and with the same patient numbers in both treatment arms) showed similar results, as the median time to deterioration was 5.6 months (95% CI: 3.8, NA) in the TAS-102 arm (N=288) vs. 4.6 months (95% CI: 2.2, NA) in the placebo arm (N=130; HR=0.97; 95% CI: 0.635, 1.470; p=0.8709 [2-sided]).

Ancillary analyses

The interim analysis (see section **Statistical methods** above) was performed based on 220 events (deaths) reported as of 31-Aug-2017 and the associated efficacy boundary suggested to the DMC was a 1-sided p-value of 0.0031 and the associated futility boundary was OS HR ≥0.95. The observed HR, based on 200 events, was 0.7321 (95% CI: 0.5540, 0.9676; 1-sided p-value 0.0138). The associated mOS was 5.7 months for the TAS-102 group and 3.8 months for the placebo group. An additional sensitivity analysis was presented based on all events (deaths) reported as of the date of the 192nd death (194 deaths were reported

as of that date). The corresponding efficacy boundary for the sensitivity analysis was 1-sided p-value of 0.0016. Neither the efficacy nor futility boundaries were met for any of the analyses and the DMC recommended to continue the study until completion, per protocol. Considering the alpha-spending that took place for the interim analysis, the associated efficacy boundary for the final analysis (assuming 384 events as planned) is 1-sided p-value of 0.0215.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 20. Summary of efficacy for study TAS-102-302 (TAGS)

Title: Randomized, double-blind, phase 3 study evaluating TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer refractory to standard treatments			
Study identifier	TAS-102-302; NCT02500043; EudraCT Number: 2015-002683-16		
Design	Global, multicentre, randomized (2;1), parallel, double-blind, placebo-controlled		
	Date first patient was randomized: Date last patient was randomized: Duration of treatment:		24-Feb-2016 05-Jan-2018 Patients were treated until there was evidence of disease progression, unacceptable toxicity, one of the other discontinuation criteria was met or until completion of the primary endpoint, whichever occurred first.
Hypothesis	Superiority		
Treatments groups	**TAS-102**		TAS-102 35 mg/m2 twice daily *per os* on days 1-5 and 8-12 of 28-day cycles + best supportive care (BSC) N = 337 (intention-to-treat [ITT] population)
	Placebo		Placebo tablets twice daily *per os* on days 1-5 and 8-12 of 28-day cycles + BSC N = 170 (intention-to-treat [ITT] population)
Endpoints and definitions	Primary endpoint	Overall survival (**OS**)	Time from the date of randomization to the date of death due to any cause
	Key secondary endpoint	Progression-free survival (**PFS**)	Time from the date of randomization until the first date of investigator-assessed radiological disease progression or death due to any cause
	Other secondary endpoint	Objective response rate (**ORR**)	Proportion of patients with an investigator-assessed complete response (CR) or partial response (PR)
	Other secondary endpoint	Disease control rate (**DCR**)	Proportion of patients with an investigator-assessed CR, PR or stable disease (SD)
	Other secondary endpoint	**Time to deterioration to** Eastern cooperative oncology group performance status (**ECOG PS**) **≥2**	Time from randomization until the first date on which an ECOG PS ≥2 was observed

	Other secondary endpoint	**Time to deterioration of** quality of life (**QoL**) **by ≥5 points**	Time from randomization until the first date on which a deterioration of QoL by ≥5 points in global health status was observed, as measured using the European organisation for research and treatment of cancer QoL questionnaire - core 30 (EORTC QLQ-C30) and QoL questionnaire - gastric cancer-specific module (QLQ-STO22)
Database lock	The target number of events, i.e. 384 deaths, was reached on 27-Mar-2018, which is thus the OS data cut-off date. The cut-off date for all other (non-OS) clinical data was 31-Mar-2018.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population Data cut-off date for OS 27-Mar-2018 Data cut-off date for all other (non-OS) clinical data 31-Mar-2018		
Descriptive statistics and estimate variability	Treatment group	TAS-102	Placebo
	Number of subject	337	170
	Median **OS** (months)	5.7	3.6
	95% confidence interval (CI)	4.8, 6.2	3.1, 4.1
	Median **PFS** (months)	2.0	1.8
	95% CI	1.9, 2.3	1.7, 1.9
	ORR (%)	4.5	2.1
	95% CI	2.4, 7.5	0.4, 5.9
	DCR (%)	44.1	14.5
	95% CI	38.3, 50.1	9.2, 21.3
	Median **time to deterioration to ECOG PS ≥2** (months)	4.3	2.3
	95% CI	3.7, 4.7	2.0, 2.8
	Median **time to deterioration of QoL by ≥5 points** (months)	2.6	2.3
	95% CI	2.3, 3.3	1.4, NA
Effect estimate per comparison	**OS**	Comparison groups	TAS-102 vs. placebo
		Hazard ratio (HR)	0.69
		95% CI	0.560, 0.855
		P-value (1-sided)	0.0003 (efficacy boundary 0.0215)
	PFS	Comparison groups	TAS-102 vs. placebo
		HR	0.57
		95% CI	0.467, 0.701
		P-value (2-sided)	<0.0001
	ORR	Comparison groups	TAS-102 vs. placebo
		Difference	+2.4
		95% CI	-0.9, 5.7
		P-value (2-sided)	0.2833
	DCR	Comparison groups	TAS-102 vs. placebo
		Difference	+29.7
		95% CI	21.6, 37.7
		P-value (2-sided)	<0.0001
	Time to deterioration of	Comparison groups	TAS-102 vs. placebo
		HR	0.69

	ECOG PS ≥2	95% CI	0.562, 0.854
		P-value (2-sided)	0.0005
	Time to deterioration of QoL by ≥5 points	Comparison groups	TAS-102 vs. placebo
		HR	1.27
		95% CI	0.854, 1.875
		P-value (2-sided)	0.2350
Notes	For the other secondary endpoints **ORR** and **DCR** the tumour response (TR) population was used, comprised of 290 TAS-102-treated patients and 145 placebo-treated patients. For the other secondary endpoint **time to deterioration of QoL** the study arms were comprised of 288 TAS-102-treated patients and 130 placebo-treated patients.		

Abbreviations: NA = not available

Clinical studies in special populations

The below table shows the number of elderly patients in the TAGS study, further specified per age category (i.e. age 65-74, age 75-84, and age 85+). Refer also to the forest plot of OS subgroup analyses (Figure 4).

	Age 65-74 (older subjects number/total number)	**Age 75-84 (older subjects number/total number)**	**Age 85+ (older subjects number/total number)**
Controlled trials	159 / 507 (31.4%)	67 / 507 (13.2%)	2 / 507 (0.4%)
Non-controlled trials	NA	NA	NA

Note: the only controlled trial was study TAS-102-302 (TAGS).

Supportive study(ies)

No supportive study(ies) was/were submitted by the applicant.

2.4.3. Discussion on clinical efficacy

Dose selection

The proposed TAS-102 starting dose in adult patients with mGC is 35 mg/m^2 administered BID PO on days 1 to 5 and days 8 to 12 of each 28-day cycle, which is to be continued as long as benefit is observed or until unacceptable toxicity occurs. This posology is identical to that previously accepted for treatment of adult patients with mCRC, in which the 35 mg/m^2 dose was selected based on tolerability in patients with mCRC and other solid tumours. Though the support of the dose in mGC patients is limited, especially with regard to efficacy, no apparent differences are observed with respect to safety between mCRC and mGC patients treated at the proposed dose.

Design and conduct of clinical studies

Study design. The randomised, double-blind, placebo-controlled design that was used in the pivotal study TAS-102-302 is considered adequate to evaluate the benefits and risks of TAS-102 in patients with mGC refractory to standard treatments, i.e. in the third- and later-line treatment setting. The choice for OS as the primary endpoint of the pivotal study is considered appropriate. Firstly, as convincingly demonstrated favourable effects on OS are from both a clinical and methodological perspective the most persuasive outcome of a clinical trial (EMA/CHMP/205/95 Rev.5). Secondly, it is considered appropriate specifically for this target patient population, considering the short life expectancy. The study design also included the key secondary endpoint PFS and the other secondary endpoints ORR and DCR. All these imaging endpoints were assessed by the investigators according to RECIST 1.1 criteria. No (blinded) central evaluation of imaging

was performed. As OS was the primary endpoint and the effect on OS will be most important in the assessment of efficacy, this lack of central evaluation of imaging for the imaging endpoints is considered acceptable.

Various second-line treatment options are used sequentially in second- and third-line in clinical practice for the small proportion of GC patients that is eligible for third-line treatment. On this matter, the ESMO guidelines concur, but indicates caution that "there is no clear evidence for a benefit beyond second-line treatment" (Smyth, 2016).

According to the study protocol, QoL assessments were performed prior to study treatment administration in each cycle. However, the applicant was not able to confirm that the QoL questionnaires were completed at the beginning of each visit, prior to *any* clinical activities (i.e. before any extensive contact and consultation with study site personnel). As a result, the patient responses may have been biased, as e.g. medical information could bias retrospective evaluation (EMA/CHMP/292464/2014).

Patient population. The inclusion and exclusion criteria for the pivotal study appear overall acceptable. The patient population enrolled in study TAS-102-302 appears to be a somewhat selected population compared to patients with mGC treated in clinical practice in the sense that patients had to have an ECOG PS ≤1. Certainly not all European patients with mGC after first-line systemic treatment are expected to demonstrate a score ≤1, whereas over one third of enrolled patients even had a score of 0. This is adequately reflected by the current proposed text in the SmPC.

Statistical analysis. Analyses were performed as outlined in the SAP and were appropriate given the type of endpoints. The IA was performed at a slightly higher number of events than planned, but the efficacy boundary for the final analysis was adjusted accordingly.

It is noted that for the analysis of ORR and DCR the TR population was used instead of the ITT population. This analysis may be biased as it only included patients with at least one post-baseline assessment. However, given the low number of responders (TAS-102: 13; placebo: 3) this issue is considered not worth pursuing.

For the endpoint time to deterioration of QoL, patients with no deterioration in the QoL scores were censored at death date. The applicant later provided the results of additional sensitivity analyses wherein death was included as an event, and the results of these analyses were consistent with the results of the original analyses.

Efficacy data and additional analyses

The demographics and other baseline characteristics were in general reasonably well balanced between both treatment arms, and no particularities were observed. There were amongst others slightly more males, slightly more patients ≥75 years of age, slightly more white patients, and slightly more patients with an ECOG PS of 1 in the TAS-102 arm (n=337) when compared to the placebo arm (n=170). The number of enrolled patients from the EU was 277 (54.6% of the ITT population; 180 in the TAS-102 arm and 97 in the placebo arm). The region subgroup analyses for OS and PFS were consistent.

The baseline disease characteristics were in general reasonably well balanced between both treatment arms as well. It is noted that over half of the enrolled patients' tumours had the histology subtype "Unknown" or "Not applicable". Importantly, the efficacy of TAS-102 does not appear to differ (much) between the histology subtypes "Diffused", "Intestinal", and "Unknown or NA", see Figure 1 and Figure 6 above. The performed **multivariate sensitivity analysis** (for OS) in which adjustment was made for possible prognostic baseline factors, showed a result (HR) fully in line with the primary OS analysis. Therefore, the slight imbalances in possible prognostic baseline factors apparently did not have a relevant impact on the primary efficacy analysis.

Of the ITT population, 43.6% had undergone a prior gastrectomy. This percentage is similar to the percentages reported in other recent studies in mGC that enrolled a mostly non-Asian patient population (Cyramza EPAR: 26.8% and 37.1%; Shitara, 2018: 36.8%).

Ramucirumab, an approved second-line treatment, had been used by only 33.3% of patients in the ITT population. However, ramucirumab treatment was a stratification factor, and similar proportions of patients in each treatment group had received it. Moreover, efficacy did not differ much between patients that did and patients that did not receive prior ramucirumab treatment.

Remarkably, the HER2 status at baseline was not known/available for almost one in five patients in the pivotal study (i.e. 19.5%). Furthermore, in spite of inclusion criterion #3 (sub. a.) not all patients with HER2+ tumours had received previous anti-HER2 therapy. Use of previous anti-HER2 therapy might not have been available to all patients or possible in some patients because of comorbid conditions (e.g., cardiac disease). Reasons for withholding anti-HER2 therapy were not gathered. The abovementioned multivariate sensitivity analysis did identify baseline HER2 status as a prognostic/predictive factor. As HER2+ status in GC may be associated with a worse prognosis (van Cutsem, 2016), and more patients in the TAS-102 arm than in the placebo arm were baseline HER2+, this factor is unlikely to have positively influenced the TAS-102 efficacy results. Not surprisingly, prior anti-HER2 therapy was also more frequent in the TAS-102 arm, but efficacy did not seem to be dependent on baseline HER2 status.

Considering the demographics and other baseline (disease) characteristics, there are overall no critical issues regarding the enrolled patient population, which appears reasonably representative of the to-be-treated patient population in clinical practice, apart from the remark made above on ECOG PS.

Primary endpoint – OS. The effect of TAS-102 on OS relative to placebo resulted a HR of 0.69 (95% CI: 0.560, 0.855,; p=0.0003), with mOS of 5.7 months for TAS-102 versus 3.6 months for placebo, reflecting an increase in mOS of 2.1 months. The results of all sensitivity analyses were consistent with this primary analysis of OS. Moreover, there were no notable differences between arms in terms of the proportion of patients receiving PDT and/or the type(s) of PDT received, which adds robustness to the study results.

In the subgroup analyses the OS HRs almost consistently favoured the TAS-102 group, e.g. the number of prior (systemic) treatment regimens and the primary tumour site (GEJ vs. gastric) had little effect on the HR point estimate.

The only two exceptions (of the 49 subgroups examined) were the subgroups of patients who had not received prior taxane therapy and the subgroup of patients with well differentiated tumours. For both subgroups the number of patients was limited (<10% of the ITT population) and the PFS HR did favour the TAS-102 arm, which speaks in favour of these exceptions likely being chance findings. Moreover, an additional unstratified sensitivity analysis showed an OS HR of 0.99 (95% CI: 0.50, 1.97) in the subgroup of patients with no prior taxane use, and 0.98 (95% CI: 0.49, 1.95) in the patients with well differentiated tumours.

A (prior) gastrectomy could alter the PK and pharmacodynamics of orally administered chemotherapeutic agents such as TAS-102 (Shitara, 2018). Unfortunately, PK data were not recorded in this study. The PK of TAS-102 were assessed in the phase 2 EPOC1201 study and moreover compared between patients who had undergone a gastrectomy and those who had not (Bando, 2016). There were no significant differences in the peak serum drug concentration (C_{max}), area under the plasma drug concentration-time curve (AUC), and/or time of peak serum drug concentration (T_{max}) values for FTD and TPI at the 35 mg/m^2 BID dosage when three patients with and three patients without a prior gastrectomy were compared, and in another six patients (two with, four without prior gastrectomy) at the 40 mg/m^2 dose. Despite the fact that this PK data is obtained from a relatively small number of patients, data do not point at the existence of major differences in FTD and/or TPI PK between patients with or without a prior gastrectomy. The fact that no relevant pH dependence of FTD and/or TPI PK is known intuitively supports this assumption. Reassuring is that both in

patients that did undergo a prior gastrectomy (HR=0.57; 95% CI: 0.41, 0.79) as well as in patients that did not (HR=0.80; 95% CI: 0.60, 1.06), the OS HR favoured the TAS-102 group. Also, the above-mentioned multivariate sensitivity analysis did not identify (no) prior gastrectomy as a prognostic/predictive factor, and the PFS HR in the 'no prior gastrectomy' subgroup *did* statistically significantly favour the TAS-102 arm.

Numerically a 2.1-month mOS benefit may seem rather limited, especially because the enrolled patient population appears to be a somewhat selected population compared to patients with mGC treated in clinical practice (which e.g. may be more frail with a higher ECOG PS and possibly with more comorbidity). On the other hand, in Europe there is currently no therapy with proven OS or other clinical benefit. Therefore, in combination with the overall poor prognosis of mGC patients, the observed gain in mOS is considered clinically relevant.

Key secondary endpoint – PFS. A statistically significant benefit was also shown for the key secondary endpoint PFS. Treatment with TAS-102 when compared to placebo resulted in a HR of 0.57 (95% CI: 0.467, 0.701; p<0.0001), with mPFS of 2.0 months for TAS-102 versus 1.8 months for placebo, reflecting an increase in mPFS of 0.2 months. The results of all relevant sensitivity analyses were consistent with this primary analysis of PFS. Of note, as is stated above, the primary analysis of PFS was not in accordance with EMA guidance, but one of the sensitivity analyses was and it showed consistent results.

In the subgroup analyses the PFS HRs favoured the TAS-102 group across all subgroups examined.

The observed PFS result *does* provide support for the observed OS result.

Other secondary endpoints – ORR and DCR. The ORR was numerically (but not statistically significantly) higher in patients in the TAS-102 arm as compared to the placebo arm (4.5% vs. 2.1%, respectively, p=0.2833). Due to the many patients with SD in the TAS-102 arm, there was a statistically significant improvement in the DCR when compared to the placebo arm (44.1% vs. 14.5%, respectively; p<0.0001). These results are in line with the OS data.

Other secondary endpoint – time to deterioration to ECOG PS ≥2. Treatment with TAS-102 resulted in a statistically significant increase in the median time to deterioration to ECOG PS ≥2 compared to placebo (HR=0.69; 95% CI: 0.562, 0.854; p=0.0005; 4.3 vs. 2.3 months, respectively). This is considered a relevant outcome from the clinical point of view, supportive of the overall good tolerability and acceptable safety profile of TAS-102 in this clinical context.

Other secondary endpoint – time to deterioration of QoL. No statistically significant differences in the time to deterioration of QoL scores (by ≥5 or ≥10 points) between TAS-102 and placebo groups were observed. More importantly however, the QoL assessment was severely hampered by the rapidly declining compliance and (as a result) many missing values in both treatment arms, even though this is in part a reflection of the high rate of progression and therefore not unexpected. Therefore, no clear conclusions can be made on the basis of the QoL data submitted.

Special populations. *Paediatric patients:* The EMA confirmed the applicability of the class waiver for TAS-102 in GC. No data in paediatric patients have thus been submitted. *Elderly patients:* the pivotal study included 228 (45.0%) patients ≥65 and 69 (13.6%) patients ≥75 years of age. The OS subgroup analyses showed that efficacy (i.e. the HR) was similar regardless of age category, see Figure 4.

2.4.4. Conclusions on the clinical efficacy

In the single pivotal study, TAS-102 treatment (n=337) conferred a statistically significant, and clinically relevant mOS benefit of 2.1 months over placebo (n=170; HR=0.69; 5.7 vs. 3.6 months; p=0.0003) in the third- or later-line mGC setting. This OS result was robust and supported by a statistically significant benefit in PFS (HR=0.57; 2.0 vs. 1.8 months; p<0.0001), a trend in ORR (4.5% vs. 2.1%; p=0.2833), and a statistically significant benefit in DCR (44.1% vs. 14.5%; p<0.0001). Therefore, in spite of this being an

application based on a single pivotal study, the efficacy results are considered quite convincing. In addition, considering that there is currently no approved third- or later-line therapy for patients with mGC, and the non-approved therapies currently used in clinical practice are given without proof of OS benefit, the observed gain in mOS of 2.1 months is considered clinically relevant.

2.5. Clinical safety

Introduction

The known adverse drug reactions (ADRs) observed for Lonsurf (TAS-102) at rates ≥1/10 are neutropenia, leukopenia, anaemia, thrombocytopenia, decreased appetite, diarrhoea, nausea, vomiting, and fatigue.

The safety data in the current application of TAS-102 for the treatment of mGC are derived from the pivotal study TAGS only. The respective study concerns a randomized, controlled, double-blind Phase 3 study in which the effects of TAS-102 plus best supportive care (hereafter: TAS-102) were compared with those of placebo plus best supportive care (hereafter: placebo) in patients with mGC who had received at least 2 prior regimens for advanced disease and who were refractory to or unable to tolerate their last prior therapy.

Standard safety monitoring was performed, and adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Safety assessments also included the evaluation of laboratory test results, vital signs measurements, physical examination findings, and changes in ECOG PS score.

Below, collected safety data on TAS-102 in the TAGS study in mGC will be compared with the known safety profile of TAS-102 in the RECOURSE study in mCRC (Lonsurf mCRC EPAR). The safety data cut-off for TAGS was 31-Mar-2018 and for RECOURSE 31-Jan-2014.

Patient exposure

Study data from TAGS are presented for the as-treated (AT) population, consisting of all patients who received at least one dose of study therapy. The AT population comprised of 503 patients, including 335 patients who received TAS-102 and 168 who received placebo.

The patient disposition at the safety data cut-off date is summarised below in Table 21. The majority of patients in both arms had discontinued treatment, as only 19 (5.7%) patients in the TAS-102 arm and 3 (1.8%) patients in the placebo arm were still on treatment. The most important reason for treatment discontinuation in both treatment groups was progression of disease (TAS-102 (73.0%), placebo (85.3%)). A total of 44 patients (including 33 (9.9%) in the TAS-102 arm and 11 (6.5%) in the placebo arm) discontinued study treatment due to AEs.

Table 21. **Summary of patient disposition (ITT population)**

Parameter, n (%)	TAS-102 N = 337	Placebo N = 170
Patients Randomized	337 (100)	170 (100)
Patients Treated	335 (99.4)	168 (98.8)
On Treatment	19 (5.7)	3 (1.8)
Off Treatment	316 (94.3)	165 (98.2)
Due to Progression of Disease	246 (73.0)	145 (85.3)
Due to an Adverse Event	33 (9.9)	11 (6.5)
Due to Withdrawal of Consent	14 (4.2)	4 (2.4)
Due to Patient Death	11 (3.3)	2 (1.2)

Parameter, n (%)	TAS-102 N = 337	Placebo N = 170
Due to Investigator Decision	11 (3.3)	3 (1.8)
Due to Protocol Violation	1 (0.3)	0

Abbreviations: ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

[a] Of the deaths in the TAS-102 arm, 2 were due to AEs and 9 to disease progression; in the control arm, both deaths were due to disease progression.

Overall, exposure to study treatment tended to be higher in the TAS-102 study arm (median: 6.71 weeks) compared to the placebo study arm (median: 5.71 weeks), see Table 22. The number of initiated cycles per study patient tended to be higher in TAS-102-treated study patients compared to placebo-treated study patients (mean 3.3 vs. 2.3 respectively).

Table 22. Summary of exposure by treatment group (AT Population)

	TAS-102 N = 335	Placebo N = 168
Total number of weeks of exposure[a]	4038	1191
Mean (SD)	12.05 (11.47)	7.09 (7.84)
Median	6.71	5.71
Min, Max	0.4, 62.7	0.1, 63.0
Cycles initiated per patient[b]		
Total cycles initiated	1108	394
Mean (SD)	3.3 (2.50)	2.3 (1.92)
Median	2.0	2.0
Min, Max	1,14	1,16
Cycle initiated, n (%)[b]		
1	335 (100)	168 (100)
2	282 (84.2)	125 (74.4)
3	145 (43.3)	33 (19.6)
4	116 (34.6)	18 (10.7)
>4	65 (19.4)	15 (8.9)

Abbreviations: AT = as-treated; N = number of patients in arm; n = number of patients in group; SD = standard deviation

[a] (Date of last dose of study medication – date of first dose of study medication +1) / 7
[b] Patients counted in each cycle initiated (at least 1 dose administered)

Median dose intensity was 156.72 mg/m^2/week for TAS-102-treated study patients and 166.15 mg/m^2/week for placebo-treated study patients, see Table 23. Dose intensities of provided study treatments were close to the planned dose intensities (median relative dose intensity: 0.90 for TAS-102 vs. 0.95 for placebo). Over the entire treatment period, 95.8% (320/334) of patients in the TAS-102 group and 92.3% (155/168) of patients in the placebo group received ≥90% of their target cycle dose.

Table 23. Summary of cumulative dose and dose intensity by treatment group (AT Population)

	TAS-102 N = 335	Placebo N = 168
Total dose administered, mg/m^2		
N	334	168

	TAS-102 N = 335	Placebo N = 168
Mean (SD)	2127.3 (1651.7)	1512.05 (1325.3)
Median	1387.5	1341.1
Min, Max	104.8, 9367.9	68.3, 10802.3
Dose intensity, mg/m^2/week		
N	334	168
Mean (SD)	148.2 (26.8)	155.0 (27.9)
Median	156.7	166.2
Min, Max	26.2, 177.5	17.1, 191.9
Relative dose intensity[a]		
N	334	168
Mean (SD)	0.85 (0.15)	0.89 (0.16)
Median	0.90	0.95
Min, Max	0.15, 1.01	0.10, 1.10

Abbreviations: AT = as-treated; Max = maximum; Min = minimum; N = number of patients in arm; n = number of patients in group; SD = standard deviation

[a] Ratio of actual dose intensity divided by planned dose intensity

The patients in the TAS-102 arm in the TAGS study had a similar exposure to TAS-102 when compared to the patients in the TAS-102 arm in the RECOURSE study. The median total number of weeks exposure was 6.71 weeks in both studies, and the median relative dose intensity was 0.90 in the TAGS study and 0.91 in the RECOURSE study.

Demographic and other characteristics of the study population

Overall, baseline characteristics were balanced across different treatment groups in the TAGS study, see for ITT population Table 8. Similar baseline characteristics were observed for the AT population. For example, the majority of included study patients in respective study were men (TAS-102: 74.6%, placebo: 69%). Median age was 64 years in TAS-102 treated study patients and 62 years in placebo-treated study patients. More than 50% of study patients were included in Europe. Most included study patients in the TAGS study were Caucasians (TAS-102: 72.2%, placebo: 66.7%).

Overall, baseline disease characteristics of the TAS-102 and placebo treatment groups were comparable in the TAGS study (Table 9). Performance status at baseline according to the Eastern Cooperative Oncology Group (ECOG) was 1 in 63.3% of TAS-102-treated patients and 59.5% of placebo-treated patients. All other study patients in both treatment groups had an ECOG performance status of 0.

Hepatic function was normal in 74.3% of patients treated with TAS-102 and 78.6% of patients treated with placebo. However, a slightly higher proportion of patients in the TAS-102 arm had mild hepatic impairment at baseline compared to the control arm (25.1% vs. 19.6%).

Renal function at baseline was normal (i.e. creatinine clearance ≥90 ml/min) in 40.0% of patients treated with TAS-102 and in 40.5% of patients treated with placebo. Similar proportions of patients in the TAS-102 and placebo treatment groups had mild renal impairment (i.e. creatinine clearance 60-89 ml/min)(respectively 42.1% and 42.3%), and more severe renal impairment (moderate impairment (i.e. creatinine clearance 30-59 ml/min) respectively 17.3% and 16.7%, severe impairment (i.e. creatinine clearance <30 ml/min) 0.6% in both treatment groups).

Adverse events

Definitions

Per protocol, treatment-emergent adverse events (TEAEs) are defined as AEs with onset following the first dose of study therapy (TAS-102 or placebo) and no more than 30 days after the last dose of study therapy. TEAE do not necessarily have a causal relationship to the use of study treatment. Any event considered "possibly," "probably," or "definitely" related to study therapy by the investigator will be collectively described as "related".

A distinction is made between "AEs with an outcome of death / discontinuation" and "deaths / discontinuations due to AEs", specifically:

- "AEs with an outcome of death / discontinuation" includes all AEs where the investigator-assigned outcome is "death / discontinuation." This may include events that were simply ongoing at the time of death, even if the event was not a cause of death and/or discontinuation. Note: "AEs with an outcome of death" are synonymous with "Grade 5 (fatal) events."
- "Deaths / discontinuations due to AEs" include all deaths / discontinuation where the primary cause of death or discontinuation was an AE according to the investigator.

Overview of adverse events

In the TAGS study, 97.3% of patients in the TAS-102 arm experienced TEAEs compared to 93.5% of patients in the placebo arm (Table 24). Numerical proportions of treatment-related AEs were higher in the TAS-102 treatment arm (80.9%) than in the placebo treatment arm (56.6%) as well. Overall occurrence of serious adverse events (SAEs) was similar for respective treatment groups (42.7% vs. 41.7%). However, occurrence of treatment-related SAEs tended to be higher among study patients treated with TAS-102 (11.6%) compared to those treated with placebo (3.6%).

Study treatment doses tended to be adjusted more frequently among TAS-102 treated patients (58.2%) compared to placebo treated patients (22.0%). AEs with outcome death were observed at similar rates in both treatment groups (TAS-102: 13.4%, placebo: 11.3%).

Table 24. Overview AEs in the TAGS and RECOURSE study (AT population)

	TAGS (mGC) (N=503)		**RECOURSE (mCRC) (N= 798)**	
Parameter, n (%)	**TAS-102 N = 335**	**Placebo N = 168**	**TAS-102 N = 533**	**Placebo N = 265**
Any TEAE	326 (97.3)	157 (93.5)	524 (98.3)	247 (93.2)
Any treatment-related[a] event	271 (80.9)	95 (56.6)	457 (85.7)	145 (54.7)
Any Grade ≥3 event	267 (79.7)	97 (57.7)	370 (69.4)	137 (51.7)
Any SAE	143 (42.7)	70 (41.7)	158 (29.6)	89 (33.6)
Any treatment-related[a] SAE	39 (11.6)	6 (3.6)	52 (9.8)	2 (0.6)
Any event with outcome treatment discontinuation	43 (12.8)	28 (16.7)	55 (10.3)	36 (13.6)
Any event with outcome dose modification[b]	195 (58.2)	37 (22.0)	73 (54.2)	36 (13.6)
Any event leading to any dose reduction	36 (10.7)	2 (1.2)	72 (13.5)	2 (0.8)
Any event with outcome death	45 (13.4)	19 (11.3)	17 (3.2)	30 (11.3)

	TAGS (mGC) (N=503)		RECOURSE (mCRC) (N= 798)	
Parameter, n (%)	**TAS-102 N = 335**	**Placebo N = 168**	**TAS-102 N = 533**	**Placebo N = 265**

Abbreviations: AT = as treated; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a] Relatedness per investigator assessment.
[b] "Dose modification" comprises both dose delay and dose reduction.

Overall occurrence of TEAEs and treatment-related TEAEs was comparable in the TAGS and RECOURSE study for both TAS-102 and placebo treatment (Table 24). However, occurrence of Grade ≥3 AEs, and SAEs for both treatment groups tended to occur more frequently in the TAGS study compared to the RECOURSE study. This also applies to the occurrence of AEs with outcome death during TAS-102 treatment (13.4% vs. 3.2%), but not to the occurrence of AEs with outcome death during placebo treatment (11.3% in both studies).

Common adverse events

Nearly all of the events reported with an incidence of ≥10% were reported more often in the TAS-102 arm than in the placebo arm (Table 25). Among the most frequently reported events, the largest differences between arms were observed for myelosuppressive AEs (specifically, neutropenia / neutrophil count decreased, anaemia, and leukopenia). Modest differences were observed between arms (with higher incidence in the TAS-102 arm) for some gastrointestinal disorders including nausea, vomiting, and diarrhoea, and fatigue.

Grade ≥3 events reported with the highest incidence in the TAS-102 arm of TAGS were neutropenia (23.3%), anaemia (18.8%), and neutrophil count decreased (11.3%). In each of these cases, the incidence of Grade ≥3 events was higher in the TAS-102 than the placebo arm. The only preferred term with an incidence of Grade ≥3 events greater than 5% in the TAS-102 arm of TAGS that is not already shown in Table 25 was general physical health deterioration (incidence of Grade ≥3 events 6.6% in the TAS-102 arm vs. 8.9% in the placebo arm).

Table 25. Treatment-emergent adverse events with incidence ≥ 10% in TAGS and RECOURSE study (AT population)

	TAGS (mGC)				RECOURSE (mCRC)			
	TAS-102 N = 335		Placebo N = 168		TAS-102 N = 533		Placebo N = 265	
Preferred Term, %	**All**	**Gr ≥3**	**All**	**Gr ≥3**	**All**	**Gr ≥3**	**All**	**Gr ≥3**
All Adverse Events	**97.3**	**79.7**	**93.5**	**57.7**	**98.3**	**69.4**	**93.2**	**51.7**
Anaemia	44.5	18.8	19.0	7.7	40.2	16.1	8.3	2.6
Neutropenia	38.5	23.3	3.6	0	29.3	20.1	0	0
Nausea	37.0	3.0	31.5	3.0	48.4	1.9	23.8	1.1
Decreased Appetite	34.3	8.7	31.0	6.5	39.0	3.6	29.4	4.9
Fatigue	26.6	6.9	20.8	6.0	35.3	3.9	23.4	5.7
Vomiting	24.8	3.6	20.2	1.8	27.8	2.1	14.3	0.4

	TAGS (mGC)				RECOURSE (mCRC)			
	TAS-102 N = 335		Placebo N = 168		TAS-102 N = 533		Placebo N = 265	
Preferred Term, %	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
Diarrhoea	22.7	2.7	14.3	1.8	31.9	3.0	12.5	0.4
Asthenia	19.4	4.8	23.8	6.5	18.2	3.4	11.3	3.0
Leukopenia	17.0	6.9	1.8	0	5.4	2.4	0	0
Abdominal Pain	16.4	4.2	18.5	8.9	14.8	2.1	13.6	3.8
Neutrophil Count Decreased	15.2	11.3	0.6	0	27.8	15.9	0.4	0
Constipation	13.4	1.2	14.9	2.4	15.2	0.2	15.1	1.1

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm

In both the TAGS and RECOURSE study, TEAEs tended to be reported more frequently in study patients treated with TAS-102 compared to those treated with placebo. More specifically, myelosuppressive AEs (anaemia (44.5% vs. 40.5%), neutropenia/ neutrophil count decreased (38.5/15.2% vs. 29.3/27.8%), and leukopenia (17.0 vs. 5.4%)) were reported more frequently in patients treated with TAS-102 in the TAGS study compared to the RECOURSE study.

Treatment-related adverse events

Table 26. Treatment-related treatment-emergent adverse events with incidence ≥ 5% in TAS-102 arm of TAGS and RECOURSE study (AT population)

	TAGS (mGC)				RECOURSE (mCRC)			
	TAS-102 N = 335		Placebo N = 168		TAS-102 N = 533		Placebo N = 265	
Preferred Term, %	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
All Related Events	**80.9**	**52.5**	**56.5**	**13.1**	**85.7**	**49.0**	**54.7**	**9.8**
Neutropenia	37.6	23.0	3.6	0	28.7	20.1	0	0
Anaemia	31.0	11.0	8.9	3.0	31.5	12.2	4.5	1.9
Nausea	25.4	2.1	15.5	1.2	39.4	0.9	10.9	0
Fatigue	18.8	3.0	10.1	1.2	24.8	2.1	10.2	1.9
Decreased Appetite	18.2	3.0	11.3	1.8	26.5	1.7	11.3	0
Diarrhoea	16.1	2.7	9.5	1.2	23.6	2.3	9.1	0
Leukopenia	15.5	6.9	1.8	0	4.7	2.1	0	0
Neutrophil count decreased	14.9	11.0	0.6	0	27.2	15.6	0.4	0
Vomiting	10.7	0.6	7.1	1.2	20.1	0.6	4.5	0
Asthenia	9.3	0.9	7.7	1.2	10.9	1.7	4.5	0.8
Thrombocytopenia	8.4	1.8	0.6	0	5.6	1.7	0.4	0.4
Platelet Count Decreased	7.2	1.2	3.0	0	14.4	2.4	1.5	0
WBC Count Decreased	6.9	2.7	0	0	26.3	9.8	0.4	0

	TAGS (mGC)				RECOURSE (mCRC)			
	TAS-102 N = 335		Placebo N = 168		TAS-102 N = 533		Placebo N = 265	
Preferred Term, %	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
Lymphopenia	5.4	1.2	3.6	1.8	0.6	0.2	0.4	0.4

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group

Consistent with known safety profile of TAS-102, treatment-related AEs in the TAS-102 arm were predominantly myelosuppressive and gastrointestinal in nature.
(Severe) treatment-related AEs tended to be reported more frequently in study patients treated with TAS-102 compared to placebo-treated patients, both in the TAGS and RECOURSE study. In general, treatment-related AEs were reported less frequently in TAS-102 treated patients in the TAGS study compared to the RECOURSE study (80.9% vs. 85.7%). Leukopenia (15.5% vs. 4.7%), thrombocytopenia (8.4% vs. 5.6%), and lymphopenia (5.4% vs. 0.6%) however were reported more frequently in the TAGS study compared to the RECOURSE study.

Deaths/serious adverse event/other significant events

Two analyses of death on study are presented in this section. The first summarises all deaths that occurred on study or within 30 days after the last dose of study therapy, with the primary cause of death as identified by the investigator. The second summarizes all AEs with an outcome of death, whether or not those AEs were the primary cause of death.

Summary of deaths with primary cause per investigator assessment

As of 31-Mar-2018, a total of 395 deaths were reported. A total of 104 patients died while on study treatment or within 30 days after the last dose of study treatment (Table 27). As shown in this table, the majority of on-study deaths in both arms were due to disease progression.

In total, there were 16 deaths on study treatment or within 30 days after last dose for which an AE was identified by the investigator as the primary cause of death (14 in the TAS-102 arm (4.2%); 2 in the control arm (1.2%)). Of these 16 events, 1 was considered at least possibly related to study therapy in the opinion of the investigator (1 event of toxic hepatitis in the control arm).

In addition, there was 1 death in the TAS-102 arm for which the cause of death was identified by the investigator as "Other." In this case, the patient died at home due to cardio-respiratory arrest. The investigator considered that the most probable cause of death was progressive disease; however a possible relationship to the study medication cannot be excluded. Upon review of the case, the applicant assessed that the underlying cause of death was most likely progression of GC and not the study medication. In view of the applicant, no safety signal was identified upon review of these cases.

Table 27. Summary of deaths with cause of death per investigator assessment - TAGS study (ITT population)

	TAS-102 N = 337	Placebo N = 170
Deaths on treatment or within 30 days after last dose, n (%)	62 (18.4)	42 (24.7)
Due to disease progression	47 (13.9)	40 (23.5)
Due to an adverse event	14 (4.2)	2 (1.2)
Due to a related adverse event	0	1 (0.6)
Due to other reason	1 (0.3)	0

Abbreviations: ITT = intent-to-treat; N = number of patients in arm; n = number of patients in group

Summary of adverse events with outcome death

AEs with an outcome of death reported for more than 0.5% of patients in the TAS-102 arm of TAGS (that is, for more than 1 patient) are summarized in Table 28. Respective AEs were observed in 13.4% of study patients treated with TAS-102 and in 11.3% of study patients treated with placebo. General physical health deterioration was the most common AEs with outcome death in both study treatment groups (TAS-102 5.1%, placebo 11.3%).

There were 3 patients who experienced pulmonary embolism with an outcome of death in the TAS-102 arm of TAGS (0.9%), versus 0 in the placebo arm. In all three cases, the investigator assessed the events of pulmonary embolism to be related to patient's underlying disease and not to TAS-102. In addition, 3 different patients experienced septic shock with an outcome of death in the TAS-102 arm of TAGS versus 0 in the placebo arm. None of these 3 events were assessed as related to TAS-102 by the investigator. In 1 of these cases (case 961-003), the patient developed pancytopenia post initiation of TAS-102. Though the investigator did not assess this case to be related to TAS-102, the applicant assessed that a causal role of TAS-102 for the event of septic shock cannot be excluded, since pancytopenia could be a risk factor for developing infections.

Table 28. Adverse events with outcome death, incidence >0.5% in the TAGS study (AT population)

	TAS-102 N = 335	Placebo N = 168
All events with outcome death (%)	**13.4**	**11.3**
General physical health deterioration	5.1	6.5
Pulmonary embolism	0.9	0
Septic shock	0.9	0
Acute coronary syndrome	0.6	0
Failure to thrive	0.6	0.6
Hepatic failure	0.6	0
Pleural effusion	0.6	0.6
Shock haemorrhagic	0.6	0

The occurrence of AEs with outcome death upon TAS-102 treatment tended to be higher in the TAGS study (13.4%) compared to the RECOURSE study (3.2%). Occurrence of AEs with outcome death upon placebo treatment was however similar in both studies (11.3%).

Other serious adverse events

SAEs reported for >1% of patients in the TAS-102 arm of TAGS are summarized in Table 29. The incidence of SAEs was similar between arms (42.7% vs. 41.7% for the TAS-102 and control arms, respectively). The most common SAE in both arms was general physical health deterioration, generally secondary to progression of disease; this preferred term was reported for 6.3% of patients in the TAS-102 arm and 8.9% of patients in the control arm. SAEs at an incidence of >1% in the TAS-102 treatment group that were reported more than 1% more frequently in the TAS-102 treatment group compared to the placebo treatment group in the TAGS study were anaemia (3.9% vs. 2.4%), pancytopenia (2.1% vs. 0%), (febrile) neutropenia (1.2% vs. 0%), neutropenic sepsis (1.2% vs. 0%), vomiting (2.7% vs. 0.6%), and diarrhoea (1.8% vs. 0%), i.e. myelosuppressive and gastro-intestinal AEs. These AEs also tended to be observed more frequently in the TAS-102 arm compared to the placebo arm in previous RECOURSE study.

Table 29. Serious adverse events, incidence >1% in the TAS-102 arm of the TAGS study (AT population)

Parameter, %	TAS-102 N = 335	Placebo N = 168
All Serious Adverse Events	**42.7**	**41.7**
General Physical Health Deterioration	6.3	8.9
Anaemia	3.9	2.4
Decreased Appetite	3.3	2.4
Vomiting	2.7	0.6
Abdominal Pain	2.4	3.6
Pancytopenia	2.1	0
Diarrhoea	1.8	0
Dysphagia	1.8	1.2
Pleural Effusion	1.5	0.6
Pulmonary Embolism	1.5	1.2
Dyspnoea	1.2	1.2
Febrile Neutropenia	1.2	0
Gastrointestinal Haemorrhage	1.2	0.6
Intestinal Obstruction	1.2	1.8
Neutropenia	1.2	0
Neutropenic Sepsis	1.2	0
Pneumonia	1.2	1.2

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group

Treatment-related SAEs were reported for 11.6% of patients in the TAS-102 treatment group and 3.6% in the placebo group (Table 30). The only treatment-related SAE occurring at an incidence of ≥2.0% in either treatment group was pancytopenia (2.1% in the TAS-102 arm vs. 0% in the control arm; all Grade 3 or higher). Related SAEs affecting more than 1 patient (≥0.6%) in the TAS-102 arm of TAGS were almost entirely myelosuppressive or gastrointestinal in nature. Similar trends were observed in previous RECOURSE study.

Table 30. Treatment-related serious adverse events in the TAS-102 treatment arm in the TAGS study (AT population)

Parameter, %	TAS-102 N = 335	Placebo N = 168
All Related SAEs	**11.6**	**3.6**
Pancytopenia	2.1	0
Anaemia	1.8	1.2
Diarrhoea	1.8	0
Febrile Neutropenia	1.2	0
Neutropenia	1.2	0
Neutropenic Sepsis	1.2	0
Decreased Appetite	0.6	0
Ileus	0.6	0
Pyrexia	0.6	0
Vomiting	0.6	0
Acute Kidney Injury	0.3	0
Alkalosis Hypochloraemic	0.3	0
Cardiorespiratory Arrest	0.3	0
Cerebrovascular Accident	0.3	0
Clostridium Difficile Colitis	0.3	0
Gastric Haemorrhage	0.3	0
Gastrointestinal Haemorrhage	0.3	0
General Physical Health Deterioration	0.3	0
Infection	0.3	0
Myocardial Infarction	0.3	0
Neutrophil Count Decreased	0.3	0
Nausea	0.3	0
White Blood Cell Count Decreased	0.3	0

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group; SAE = serious adverse event

Other significant events

Adverse events of special interest

AEs of special interest include myelosuppressive (neutropenia, anaemia, thrombocytopenia, leukopenia) and gastrointestinal AEs (nausea, vomiting, diarrhoea), which are known adverse reactions of TAS-102.

Myelosuppression

An overview of myelosuppressive AEs and laboratory abnormalities is provided in Table 31.
Haematologic AEs/ laboratory abnormalities were generally manageable when they occurred. Patients affected by neutropenia Grade 3 or 4 had a median time to recovery (i.e. to Grade <2 or ≤ baseline Grade) of 8 days. In TAGS, haematologic AEs with an outcome of treatment discontinuation were reported for only 4 patients (1.2%) in the TAS-102 arm: 1 patient with Grade 4 thrombocytopenia, 1 patient with Grade 3

thrombocytopenia, 1 patient with Grade 3 anaemia, and 1 patient with both Grade 4 neutropenia and Grade 4 thrombocytopenia.

The incidence of febrile neutropenia was low (n=6 [1.8%] in the TAS-102 arm, vs. 0 in the placebo arm). All cases of febrile neutropenia resolved with supportive treatment and none necessitated discontinuation of study therapy.

A total of 4 additional patients (1.2%) experienced events of neutropenic sepsis (Grade 3 in all cases). While all of these patients resolved/recovered with supportive treatment, the event of neutropenic sepsis had an outcome of treatment discontinuation for 2 patients (0.6%).

Supportive treatment (mainly granulocyte-colony stimulating factor [G-CSF]) for neutropenia was required for 58 patients in the TAS-102 arm (17.3%) and 3 patients in the placebo arm (1.8%).

Table 31. Overview of myelosuppressive events in the TAGS study

	TAS-102 N = 335		**Placebo N = 168**	
Parameter, %	**All**	**Gr ≥3**	**All**	**Gr ≥3**
SOC: Blood / Lymphatic	63.6	40.9	25.0	9.5
CT: *Neutropenia*	52.5	34.0	4.2	0
PT: Neutropenia	38.5	23.3	3.6	0
PT: Neutrophil Ct. Dec.	15.2	11.3	0.6	0
CT: *Anaemia*	44.8	19.1	19.0	7.7
PT: Anaemia	44.5	18.8	19.0	7.7
PT: Haemoglobin Dec.	0.6	0.3	0	0
CT: *Thrombocytopenia*	17.9	3.3	4.8	0
PT: Thrombocytopenia	9.9	2.1	1.2	0
PT: Platelet Ct. Dec.	8.4	1.2	3.6	0
CT: *Leukopenia*	23.3	9.3	1.8	0
PT: Leukopenia	17	6.9	1.8	0
PT: WBC Ct. Dec.	6.9	2.7	0	0
Parameter, %	**Gr 3**	**Gr 4**	**Gr 3**	**Gr 4**
Neutrophils (Low)	26.8	11.3	0	0
Haemoglobin (Low)	18.6	0	7.4	0
Platelets (Low)	4.3	1.5	0	0
Leukocytes (Low)	18.6	2.4	0	0

Abbreviations: AT = as treated; CT = consolidated term; Ct. Dec. = count decreased; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group; SAE = serious adverse event; SOC = system organ class; WBC = white blood cell

Overall incidences of all event types with respect to myelosuppression were higher in the TAS-102 arm than in the placebo arm and similar in trend compared to RECOURSE study. Reported AE rates tended to be lower in the TAGS study compared to the RECOURSE study. Moreover, differences between TAS-102 and placebo treatment tended to be smaller in the TAGS study compared to the RECOURSE study (e.g. difference TAS-102 and placebo for leukopenia: 21.3% (23.3 vs. 1.9%) in TAGS study, 32.2% (32.6 vs. 0.4%) in RECOURSE study). Granulocyte-colony stimulating factor during TAS-102 treatment was required in 17.3%

of study patients in the TAGS study compared to 9.4% of study patients in the RECOURSE study (Lonsurf mCRC EPAR).

To further assess the significance of neutropenia in TAGS, AEs in the System Organ Class (SOC) of Infections and Infestations are summarised in Table 32. As shown, the absolute occurrence of events of this type (included related events) was higher in the TAS-102 arm than in the placebo arm. The most common events reported in the TAS-102 arm of TAGS were upper respiratory tract infections (2.7%), urinary tract infections (2.7%), pneumonia (2.4%), oral Candidasis (1.8%), nasopharyngitis (1.5%), and neutropenic sepsis (1.2%).

Occurrence of severe (Grade ≥3) events (both 4.8%), or events with an outcome of treatment discontinuation (both 1.2%) was however similar in both treatment arms. The overall incidence of events with an outcome of death was low in both arms, and the difference between arms with respect to this outcome was <1%.

Table 32. Summary of events in the system organ class: Infections and Infestations - TAGS (AT population)

	TAS-102 N = 335	Placebo N = 168
SOC: Infections and Infestations (Any TEAE)	**23.3**	**15.5**
Any treatment-related event	4.5	1.2
Any Grade ≥3 event	4.8	4.8
Any related Grade ≥3 event	1.5	0
Any treatment-related SAE	1.8	0
Any event with outcome treatment discontinuation	1.2	1.2
Any event with outcome dose modification[a]	3.3	2.4
Any event with outcome death	1.5	0.6

Abbreviations: AT = as treated; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event

[a] "Dose modification" comprises both dose delay and dose reduction.

Occurrence of infections and infestations during TAS-102 treatment tended to be lower in the TAGS study (23.3%) compared to the RECOURSE study (28.0%).

Gastrointestinal toxicity

Events in the SOC of gastrointestinal disorders are summarised in Table 33. The overall incidence of events in this SOC tended to be higher in the TAS-102 than in the placebo arm of TAGS (72.8% vs. 67.3%). Severe (Grade ≥3) AEs (20.9% vs. 28.6%) and treatment discontinuation due to AEs (4.5 vs. 6.5%) did not tend to be higher in the TAS-102 arm compared to the placebo arm.

Table 33. Summary of events in the system organ class gastrointestinal disorders - TAGS study (AT Population)

	TAS-102 N= 335	Placebo N= 168
SOC: Gastrointestinal Disorders (Any TEAE)	**72.8**	**67.3**
Any serious event	16.4	18.5
Any treatment-related SAE	3.3	0.6
Any Grade ≥3 event	20.9	28.6
Any treatment-related event	41.2	29.8
Any related Grade ≥3 event	5.4	3.6
Any event with outcome treatment discontinuation	4.5	6.5
Any event with outcome dose modification[a]	14.3	10.7
Any event with outcome death	0.6	1.8

[a] "Dose modification" comprises both dose delay and dose reduction.

Events of nausea, vomiting, and diarrhoea are summarised in Table 34. A total of 54.9% of patients in the TAS-102 arm and 45.8% of patients in the placebo arm reported nausea, diarrhoea, and/or vomiting. The difference between arms in the incidence of Grade ≥3 events was much smaller (7.2% vs. 6.0%). Incidence of nausea, vomiting, or diarrhoea with an outcome of treatment discontinuation was similar between arms (1.5% vs. 1.8%). Overall, increases in the occurrence of diarrhoea, nausea, and vomiting in the TAS-102 arm in comparison to placebo arm is less pronounced compared to what was observed in the previous RECOURSE study (Lonsurf mCRC EPAR).

Table 34. Treatment-emergent adverse events of nausea, vomiting, and diarrhoea - TAGS study (AT Population)

	TAS-102 N = 335		Placebo N = 168	
Parameter, %	**All**	**Gr ≥3**	**All**	**Gr ≥3**
Any Event	**54.9**	**7.2**	**45.8**	**6.0**
PT: Diarrhoea	22.7	2.7	14.3	1.8
PT: Nausea	37.0	3.0	31.5	3.0
PT: Vomiting	24.8	3.6	20.2	1.8

Abbreviations: CT = consolidated term; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; PT = preferred term; SOC = system organ class

Analysis of adverse events by organ system or syndrome

Liver impairment-related adverse events

Events in the SOC of hepatobiliary disorders are summarized in Table 35. AEs related to liver impairment were reported in <10% of study patients and rarely resulted in an outcome of death (0.6% in both arms) or treatment discontinuation (0.6% in both arms). Similar trends had been observed in the RECOURSE study.

Table 35. Overview of hepatobiliary disorders - TAGS and RECOURSE study (AT population)

Preferred term, %	TAGS (mGC)		RECOURSE (mCRC)	
	TAS-102 N = 335	Placebo N = 168	TAS-102 N = 533	Placebo N = 265
All Events in SOC	**7.5**	**6.0**	**10.3**	**10.6**
Events with Outcome Death	0.6	0.6	0.4	3.0
PT: Hepatic Failure	0.6	0	0.4	2.3
PT: Hepatitis Toxic	0	0.6	0	0
Events with Outcome Treatment Discontinuation	0.6	0.6	0.9	3.0
PT: Hepatic Failure	0.3	0	0	1.1
PT: Hyperbilirubinaemia	0.3	0	0.4	0.4
PT: Jaundice	0	0.6	0.4	0.8

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group; PT = preferred term; SOC = system organ class

Renal impairment-related adverse events

Events in the SOC of renal and urinary disorders occurred slightly more frequently in the placebo arm (6.0%) than in the TAS-102 arm (5.4%). Grade ≥3 events were very rare (incidence 0.3% and 1.2% in the TAS-102 and placebo arms, respectively), and no events leading to outcomes of death or treatment discontinuation were reported.

In the TAGS study, proteinuria occurred in 2 patients (0.6%) in TAS-102 arm and none in placebo arm. All were Grade 1 or 2. Treatment-related proteinuria occurred only in 1 patient (0.3%) in TAS-102 arm and was limited to a Grade 1, and none occurred in the placebo arm.

In Table 41 the occurrence of AEs by creatinine clearance at baseline is presented.

Laboratory findings

Haematology

Table 36 summarises Grade 3 (severe) or 4 (potentially life threatening) haematologic laboratory abnormalities for selected parameters, including all instances where a parameter worsened by at least one Grade from baseline. As shown, the overall incidences of these event types were generally higher in the TAS-102 arm than in the placebo arm.

Table 36. Grade 3-4 haematologic laboratory abnormalities worsening by at least 1 grade from baseline - TAGS study (AT population)

Laboratory Finding, %	TAS-102 N = 335		Placebo N = 168	
	Gr 3	Gr 4	Gr 3	Gr 4
Neutropenia (neutrophils low)	26.8	11.3	0	0
Anaemia (haemoglobin low)	18.6	0	7.4	0
Leukopenia (leukocytes low)	18.6	2.4	0	0
Lymphopenia (lymphocytes low)	16.8	2.1	8.0	0
Thrombocytopenia (platelets low)	4.3	1.5	0	0

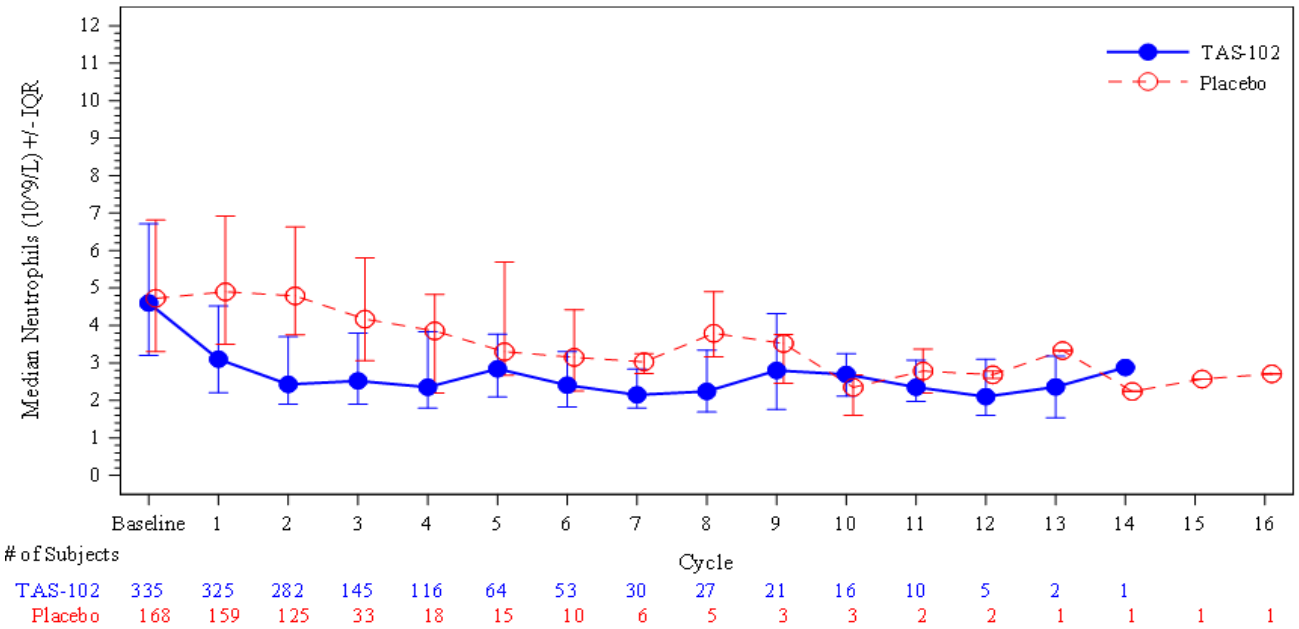
Abbreviations: AT = as treated; Gr = Grade; N = number of patients in arm

Neutrophils

In the TAS-102 arm, 88 (26.8%) patients experienced Grade 3 and 37 (11.3%) experienced Grade 4 neutrophil decreases, while no Grade 3 or 4 values were observed in the placebo arm.

Median neutrophil count at the end of each cycle (last value obtained in each cycle) was lower in the TAS-102 arm than in the placebo arm. In the TAS-102 arm, neutrophil count decreased from baseline, and remained relatively stable throughout the treatment period (figure 7). Of note, the number of study patients decreased with each subsequent study treatment cycle.

Figure 7. Median neutrophil count by cycle and treatment group TAGS study (AT population)



Serum chemistry

Table 37 summarises Grade 3 or 4 serum chemistry laboratory abnormalities for selected parameters, including all instances where a parameter worsened by at least one grade from baseline. There were no notable differences between arms for most parameters. The incidence of Grade 3 or 4 hypokalaemia that worsened from baseline was however higher in the TAS-102 arm (2.4%) than in the placebo arm (0.6%).

Table 37. Grade 3-4 serum chemistry abnormalities - TAGS study (AT population)

Parameter Low/High Value Cycle	TAS-102 N = 335		Placebo N = 168	
	N	Grades 3-4 n (%)	N	Grades 3-4 n (%)
Alanine aminotransferase (U/L) (high value)				
Baseline	335	0	168	0
All Cycles	327	8 (2.4)	161	5 (3.1)
Albumin (g/L) (low value)				
Baseline	329	4 (1.2)	167	2 (1.2)
All Cycles	327	12 (3.7)	161	4 (2.5)
Alkaline Phosphatase (U/L) (high value)				
Baseline	333	8 (2.4)	167	3 (1.8)
All Cycles	327	32 (9.8)	162	14 (8.6)
Aspartate Aminotransferase (U/L) (high value)				
Baseline	335	0	168	0
All Cycles	326	13 (4.0)	161	8 (5.0)
Bilirubin (µmol/L) (high value)				
Baseline	335	0	167	1 (0.6)
All Cycles	327	22 (6.7)	162	10 (6.2)
Calcium (mmol/L) (low value)				
Baseline	330	2 (0.6)	165	0
All Cycles	323	9 (2.8)	160	2 (1.3)
Creatinine (µmol/L) (high value)				
Baseline	335	0	168	0
All Cycles	328	2 (0.6)	162	0
Glucose (mmol/L) (low value)				
Baseline	333	0	167	0
All Cycles	326	3 (0.9)	160	0
Glucose (mmol/L) (high value)				
Baseline	333	4 (1.2)	167	1 (0.6)
All Cycles	326	4 (1.2)	160	4 (2.5)
Potassium (mmol/L) (low value)				
Baseline	334	1 (0.3)	168	3 (1.8)
All Cycles	328	8 (2.4)	162	1 (0.6)
Potassium (mmol/L) (high value)				
Baseline	334	1 (0.3)	168	0
All Cycles	328	4 (1.2)	162	1 (0.6)
Sodium (mmol/L) (low value)				
Baseline	334	6 (1.8)	168	2 (1.2)
All Cycles	328	21 (6.4)	161	18 (11.2)

Abbreviations: AT = as treated; N = number of patients in arm; n = number of patients in group

In the TAS-102 arm, the percentage of patients with elevations of ALT, AST, or both was comparable to that of the placebo arm (Table 37). Bilirubin elevations tended to be higher in the TAS-102 arm, with elevations of 1.5 x ULN reported for 14.9% (vs. 11.9% in the placebo arm) and elevations of 2 x ULN reported for 11.6% (vs. 7.1% for the control arm). Elevation of alkaline phosphatase of 1.5 x ULN was reported for 45.1% of the TAS-102 arm and 41.7% of the placebo arm.

Only in the TAS-102 arm, 2 patients met the laboratory criteria for Hy's Law (ALT or AST ≥3 x ULN; total bilirubin ≥2 x ULN; and alkaline phosphatase <2 x ULN at the same visit) vs. no patient in the placebo arm. Of note, both patients had liver metastases at baseline.

Vital signs, physical findings, and other observations related to safety

Vital signs and body weight

No clinically relevant mean or median changes in body weight or vital signs were observed in either study treatment group. Median changes from baseline at the end of each cycle were relatively stable in both treatment groups over the first several treatment cycles.

Safety in special populations and situations

Overview

Occurrence of TEAEs by age (<65 years, ≥65 years), gender, race, geographic region, ECOG PS, and baseline creatinine clearance in the TAGS and RECOURSE study are summarised in Table 38 (Integrated summary of safety). In the TAGS study, occurrence of AEs was in general higher in study patients treated with TAS-102 compared to placebo treatment. Occurrence of TEAEs during TAS-102 treatment was in general comparable for different patient features in the TAGS and RECOURSE study. Occurrence of TEAEs during both TAS-102 (98.8% vs. 96.8%) and placebo treatment (96.2% vs. 92.2%) tended to be somewhat higher for female study patients compared to male study patients in the TAGS study.
Occurrence of TEAEs in both treatment groups varied among different levels of renal impairment. However, consistent trends were neither observed in the TAGS nor the RECOURSE study.

Table 38. Subgroup analysis of treatment-emergent adverse events TAGS and RECOURSE study (Integrated summary of safety)

AE Category	TAGS study (mGC)				RECOURSE study (mCRC)			
	N	TAS-102 n (%)	N	Placebo n (%)	N	TAS-102 n (%)	N	Placebo n (%)
Age, years								
<65	182	179 (98.4)	96	91 (94.8)	299	293 (98.0)	147	137 (93.2)
≥65	153	147 (96.1)	72	66 (91.7)	234	231 (98.7)	118	110 (93.2)
Gender								
Male	250	242 (96.8)	116	107 (92.2)	326	322 (98.8)	164	152 (92.7)
Female	85	84 (98.8)	52	50 (96.2)	207	202 (97.6)	101	95 (94.1)
Race								
White	242	233 (96.3)	112	107 (95.5)	305	298 (97.7)	154	144 (93.5)
Asian	51	51 (100)	29	24 (82.8)	184	183 (99.5)	94	87 (92.6)
Other	1	1 (100)	2	2 (100)	4	4 (100)	5	5 (100)
Region								
European Union	179	172 (96.1)	96	92 (95.8)	270	266 (98.5)	131	120 (91.6)
Rest of world	156	154 (98.7)	72	65 (90.3)	263	258 (98.1)	134	127 (94.8)
ECOG performance status								
0	123	117 (95.1)	68	60 (88.2)	301	295 (98.0)	147	132 (89.8)
1	212	209 (98.6)	100	97 (97.0)	232	229 (98.7)	118	115 (97.5)
Baseline creatinine clearance								
≥ 90 ml/min	145	142 (97.9)	75	71 (94.7)	306	299 (97.7)	146	134 (91.8)
60-89 ml/min	136	132 (97.1)	70	63 (90.0)	178	177 (99.4)	90	86 (95.6)

30-59 ml/min	52	50 (96.2)	23	23 (100)	47	46 (97.9)	26	24 (92.3)

Abbreviations: AE = adverse event; ECOG= Eastern Cooperative Oncology Group; mGC= metastatic gastric cancer; mCRC= metastatic colorectal cancer; N = number of treated patients in the safety population; n = number of patients in specified category

Note: Patients may be counted in more than 1 category.

Analysis of safety data by age

In TAGS, the overall incidence of AEs (regardless of Grade or relationship to study therapy) was >89% in all age groups (Table 39). All age categories in the TAS-102 group of TAGS reported approximately 80% of patients with Grade 3 or higher AEs.

Table 39. Summary of adverse events by age interval TAGS study

	TAS-102 N= 335			**Placebo N= 168**		
	Age <65 N= 182 n (%)	**Age 65-74 N= 103 n (%)**	**Age ≥75 N= 50 n (%)**	**Age <65 N= 96 n (%)**	**Age 65-74 N= 55 n (%)**	**Age ≥75 N= 17 n (%)**
Total adverse events	179 (98.4)	97 (94.2)	50 (100)	91 (94.8)	49 (89.1)	17 (100)
Treatment-related adverse events	149 (81.9)	103 (79.6)	40 (80.0)	59 (61.5)	27 (49.1)	9 (52.9)
Grade ≥3 adverse events	145 (79.7)	82 (79.6)	40 (80.0)	60 (62.5)	28 (50.9)	9 (52.9)
Treatment-related Grade ≥3 adverse events	89 (48.9)	59 (57.3)	28 (56.0)	14 (14.6)	6 (10.9)	2 (11.8)
System organ class AEs						
Blood and lymphatic system disorders	120 (65.9)	62 (60.2)	31 (62.0)	28 (29.2)	8 (14.5)	6 (35.3)
Cardiac disorders	13 (7.1)	4 (3.9)	2 (4.0)	7 (7.3)	1 (1.8)	1 (5.9)
Congenital, familial and genetic disorders	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	2 (1.1)	3 (2.9)	1 (2.0)	1 (1.0)	0 (0)	0 (0)
Eye disorders	2 (1.1)	0	4 (8.0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	148 (81.3)	63 (61.2)	33 (66.0)	71 (74.0)	32 (58.2)	10 (58.8)
General disorders and administration site conditions	108 (59.3)	60 (58.3)	30 (60.0)	54 (56.3)	30 (54.5)	14 (82.4)
Hepatobiliary disorders	13 (7.1)	8 (7.8)	4 (8.0)	7 (7.3)	2 (3.6)	1 (5.9)
Immune system disorders	0 (0)	1 (1.0)	0 (0)	1 (1.0)	0 (0)	0 (0)
Infections and infestations	43 (23.6)	19 (18.4)	16 (32.0)	16 (16.7)	8 (14.5)	2 (11.8)
Injury, poisoning, and procedural complications	3 (1.6)	4 (3.9)	1 (2.0)	3 (3.1)	3 (5.5)	0 (0)
Investigations	76 (41.8)	41 (39.8)	28 (56.0)	28 (29.2)	17 (30.9)	3 (17.6)
Metabolism and nutrition disorders	77 (42.3)	49 (47.6)	27 (54.0)	43 (44.8)	18 (32.7)	7 (41.2)
Musculoskeletal and connective tissue disorders	32 (17.6)	12 (11.7)	5 (10.0)	13 (13.5)	5 (9.1)	3 (17.6)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	7 (3.8)	7 (6.8)	2 (4.0)	5 (5.2)	1 (1.8)	0 (0)
Nervous system disorders	27 (14.8)	17 (16.5)	10 (20.0)	14 (14.6)	5 (9.1)	0 (0)
Psychiatric disorders	17 (9.3)	7 (6.8)	4 (8.0)	12 (12.5)	5 (9.1)	2 (11.8)
Renal and urinary disorders	11 (6.0)	3 (2.9)	4 (8.0)	7 (7.3)	3 (5.5)	0 (0)
Reproductive system and breast disorders	2 (1.1)	0 (0)	0 (0)	4 (4.2)	1 (1.8)	0 (0)
Respiratory, thoracic and mediastinal disorders	37 (20.3)	24 (23.3)	10 (20.0)	22 (22.9)	8 (14.5)	3 (17.6)
Skin and subcutaneous tissue disorders	25 (13.7)	11 (10.7)	10 (20.0)	4 (4.2)	3 (5.5)	1 (5.9)
Vascular disorders	11 (6.0)	4 (3.9)	6 (12.0)	3 (3.1)	0 (0)	2 (11.8)

In the RECOURSE study in mCRC, occurrence of AEs upon TAS-102 treatment was comparable for patients aged under 65 years (98.0%), patients aged 65-74 years (98.5%), and patients aged 75 years and above (100%).

Analysis of safety data by gender

In TAGS, the overall incidence of AEs was >92% in both male and female patients, across all treatment arms. In both men and women occurrence of AEs during TAS-102 treatment was higher than during placebo treatment (Table 40). Treatment-related AEs were reported for 79.2% of male and 85.9% of female patients in the TAS-102 arm, and 56.9% and 55.8%, respectively, in the placebo arm.

Table 40. Summary of adverse events by gender TAGS study

	TAS-102		**Placebo**	
	Men N= 250 n (%)	**Women N= 85 n (%)**	**Men N= 116 n (%)**	**Women N= 52 n (%)**
Total adverse events	242 (96.8)	84 (98.8)	107 (92.2)	(96.2)
Treatment-related adverse events	198 (79.2)	73 (85.9)	66 (56.9)	29 (55.8)
Grade ≥3 adverse events	193 (77.2)	74 (87.1)	65 (56.0)	32 (61.5)
Treatment-related Grade ≥3 adverse events	123 (49.2)	53 (62.4)	13 (11.2)	9 (17.3)
System organ class AEs				
Blood and lymphatic system disorders	151 (60.4)	62 (72.9)	23 (19.8)	19 (36.5)
Cardiac disorders	12 (4.8)	7 (8.2)	5 (4.3)	4 (7.7)
Congenital, familial and genetic disorders	1 (0.4)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	6 (2.4)	0 (0)	0 (0)	1 (1.9)
Eye disorders	3 (1.2)	3 (3.5)	0 (0)	0 (0)
Gastrointestinal disorders	175 (70.0)	69 (81.2)	78 (67.2)	35 (67.3)
General disorders and administration site conditions	144 (57.6)	54 (63.5)	64 (55.2)	34 (65.4)
Hepatobiliary disorders	20 (8.0)	5 (5.9)	7 (6.0)	3 (5.8)
Immune system disorders	1 (0.4)	0 (0)	1 (0.9)	0 (0)
Infections and infestations	57 (22.8)	21 (24.7)	18 (15.5)	8 (15.4)
Injury, poisoning, and procedural complications	5 (2.0)	3 (3.5)	3 (2.6)	3 (5.8)
Investigations	112 (44.8)	33 (33.8)	24 (20.7)	24 (46.2)
Metabolism and nutrition disorders	113 (45.2)	40 (47.1)	47 (40.5)	21 (40.4)
Musculoskeletal and connective tissue disorders	35 (14.0)	14 (16.5)	15 (12.9)	6 (11.5)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	13 (5.2)	3 (3.5)	5 (4.3)	1 (1.9)
Nervous system disorders	40 (16.0)	14 (16.5)	17 (14.7)	2 (3.8)
Psychiatric disorders	18 (7.2)	10 (11.8)	15 (12.9)	4 (7.7)
Renal and urinary disorders	12 (4.8)	6 (7.1)	3 (2.6)	7 (13.5)
Reproductive system and breast disorders	1 (0.4)	1 (1.2%)	1 (0.9)	4 (7.7)
Respiratory, thoracic and mediastinal disorders	54 (21.6)	17 (20.0)	21 (18.1)	12 (23.1)
Skin and subcutaneous tissue disorders	34 (13.6)	12 (14.1)	6 (5.2)	2 (3.8)
Vascular disorders	17 (6.8)	4 (4.7)	2 (1.7)	3 (5.8)

Occurrence of AEs (97.6% vs. 98.8%) and treatment-related AEs (85.5% vs. 85.9%) during TAS-102 treatment was similar for respectively women and men in the RECOURSE study in mCRC.

Analysis of safety data by ECOG PS at baseline

The rates of AEs by ECOG PS at baseline (0 vs. 1) were in alignment with those observed in the total AT population (Table 38). As expected, patients with an ECOG PS of 0 at baseline generally had lower rates of AEs than patients with a score of 1, with the exception of AEs of special interest in the TAS-102 group (ECOG 0: 76.4%; ECOG 1: 68.4%).
The overall incidence of AEs was >88% in both ECOG PS categories and treatment groups. For the TAS-102 group, AEs were reported for 95.1% of patients with an ECOG PS of 0, and 98.6% of patients with a score of 1. For the placebo group, AEs were reported for 88.2% and 97.0%, respectively (Table 38).
Grade ≥3 AEs in the TAS-102 group were reported for 72.4% of patients with an ECOG PS of 0, and 84.0% of patients with a score of 1. For the placebo group, Grade ≥3 AEs were reported for 44.1% and 67.0%, respectively.

Analysis of safety data by creatinine clearance at baseline

In TAGS, the overall incidence of AEs was >90% for patients with normal renal function, mild, and moderate impairment in both treatment groups (Table 41; Integrated summary of safety). Overall occurrence of treatment-related AEs did not tend to increase during TAS-102 treatment with increasing rates of renal impairment at baseline (normal renal function: 97.9%; mild renal impairment: 97.1%; moderate renal impairment: 96.2%). However, AEs in the system organ classes blood and lymphatic system disorders (respectively 62.1%, 62.5%, 71.2%), metabolism and nutrition disorders (respectively 37.9%, 50.0%, 55.8%), and skin and subcutaneous tissue disorders (respectively 13.1%, 14.0%, 15.4%) tended to increase with increasing renal impairment.

Table 41. Summary of adverse events by renal function in TAGS study (Integrated summary of safety)

	TAS-102 N= 335			**Placebo N= 168**		
Baseline creatinine clearance	**Normal (creatinine clearance ≥ 90 mL/min) N= 145 n (%)**	**Mild renal impairment (creatinine clearance 60-89 mL/min N= 136 n (%)**	**Moderate renal impairment (creatinine clearance 30-59 mL/min N= 52 n (%)**	**Normal (creatinine clearance ≥ 90 mL/min) N= 75** n (%)	**Mild renal impairment (creatinine clearance 60-89 mL/min N= 70 n (%)**	**Moderate renal impairment (creatinine clearance 30-59 mL/min N= 23** n (%)
Total adverse events	142 (97.9)	132 (97.1)	50 (96.2)	91 (94.7)	63 (90.0)	23 (100)
Treatment-related adverse events	115 (79.3)	114 (83.8)	40 (76.9)	39 (52.0)	46 (65.7)	10 (43.5)
Grade ≥3 adverse events	107 (73.8)	116 (85.3)	42 (80.8)	47 (62.7)	36 (51.4)	14 (60.9)
Treatment-related Grade ≥3 adverse events	63 (43.3)	79 (58.1)	32 (61.5)	11 (14.7)	10 (14.3)	1 (4.3)
System organ class AEs						
Blood and lymphatic system disorders	90 (62.1)	85 (62.5)	37 (71.2)	71 (94.7)	63 (90.0)	23 (100)
Cardiac disorders	10 (6.9)	6 (4.4)	3 (5.8)	5 (6.7)	1 (1.4)	3 (13.0)
Congenital, familial and genetic disorders	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ear and labyrinth disorders	1 (0.7)	5 (3.7)	0 (0)	1 (1.3)	0 (0)	0 (0)
Eye disorders	3 (2.1)	2 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	108 (74.5)	97 (71.3)	37 (71.2)	54 (72.0)	42 (60.0)	17 (73.9)
General disorders and administration site conditions	86 (59.3)	77 (56.6)	33 (63.5)	45 (60.0)	37 (52.9)	16 (69.6)
Hepatobiliary disorders	10 (6.9)	11 (8.1)	3 (5.8)	9 (12.0)	0 (0)	1 (4.3)
Immune system disorders	0 (0)	1 (0.7)	0 (0)	1 (1.3)	0 (0)	0 (0)
Infections and infestations	43 (29.7)	24 (17.6)	10 (19.2)	14 (18.7)	8 (11.4)	4 (17.4)
Injury, poisoning, and procedural complications	5 (3.4)	2 (1.5)	1 (1.9)	2 (2.7)	2 (2.9)	2 (8.7)
Investigations	57 (39.3)	64 (47.1)	22 (42.3)	20 (26.7)	19 (27.1)	9 (39.1)
Metabolism and nutrition disorders	55 (37.9)	68 (50.0)	29 (55.8)	28 (37.3)	31 (44.3)	9 (39.1)
Musculoskeletal and connective tissue disorders	24 (16.6)	16 (11.8)	9 (17.3)	12 (16.0)	8 (11.4)	1 (4.3)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	7 (4.8)	8 (5.9)	1 (1.9)	2 (2.7)	3 (4.3)	1 (4.3)
Nervous system disorders	19 (13.1)	25 (18.4)	9 (17.3)	12 (16.0)	7 (10.0)	0 (0)
Psychiatric disorders	12 (8.3)	13 (9.6)	3 (5.8)	11 (14.7)	6 (8.6)	2 (8.7)
Renal and urinary disorders	7 (4.8)	7 (5.1)	3 (5.8)	5 (6.7)	2 (2.9)	3 (13.0)
Reproductive system and breast disorders	2 (1.4)	0 (0)	0 (0)	3 (4.0)	1 (1.4)	1 (4.3)
Respiratory, thoracic and mediastinal disorders	31 (21.4)	23 (16.9)	16 (30.8)	11 (14.7)	15 (21.4)	7 (30.4)
Skin and subcutaneous tissue disorders	19 (13.1)	19 (14.0)	8 (15.4)	4 (5.3)	4 (5.7)	0 (0)
Vascular disorders	8 (5.5)	11 (8.1)	2 (3.8)	2 (2.7)	2 (2.9)	1 (4.3)

In previous RECOURSE study in mCRC, ≥ Grade 3AEs (85.1% vs. 66.7% and 70.8% respectively), serious AEs (42.6% vs. 27.5% and 30.3% respectively), and dose delays (38.8% vs. 28.7% and 26.7% respectively) and reductions (23.9% vs. 11.2% and 17.6% respectively) tended to occur more frequently during TAS-102 treatment in study patients with moderate renal impairment (i.e. creatinine clearance 30-59 mL/min) compared to patients without or mild renal impairment (Lonsurf mCRC EPAR). This trend was not observed in the TAGS study.

Overdose

An AE of accidental overdose was reported for 2 study patients in the TAS-102 arm of TAGS (0.6%).

- One patient mistakenly received a total dose of 1900 mg during cycle 2, approximately 158% of the planned dose of 1200 mg. This event was recorded as a Grade 3 SAE of accidental overdose. The patient also experienced a treatment-related SAE of Grade 4 neutropenia on cycle 2, day 28, which led to an 11-day delay in the initiation of cycle 3. The patient also experienced non-serious treatment-related events of Grade 3 leukopenia and Grade 2 anaemia on the same day. The patient went on to receive a total of 6 cycles of treatment.

- One patient mistakenly received a higher-than-prescribed single dose of TAS-102 during cycle 1; although the total dose administered during cycle 1 was 1100 mg as prescribed, this event was reported as a non-serious AE of accidental overdose (with no severity grade assigned).

Discontinuation due to adverse events

Adverse events with an outcome of treatment discontinuation

A total of 43 patients in the TAS-102 arm (12.8%) and 28 patients in the placebo arm (16.7%) experienced 1 or more AEs with an outcome of treatment discontinuation. Events with an outcome of discontinuation were most common in the MedDRA SOCs of gastrointestinal disorders (4.5% [TAS-102 arm] vs. 6.5% [placebo arm]) and general disorders and administration site conditions (2.4% vs. 6.0%). There was no particular pattern to these events; no individual preferred term had an outcome of discontinuation for 1% or more of patients in the TAS-102 arm with the exception of general physical health deterioration (1.2% in the TAS-102 arm vs. 2.4% in the placebo arm).

This is in line with what was observed in RECOURSE. Events with an outcome of discontinuation were reported in 10.3% in the TAS-102 group and 13.6% in the placebo group. The most frequent AE leading to discontinuation in the TAS-102 group was general physical health deterioration (2.3% vs. 1.9% in the placebo arm).

Adverse events with outcome of treatment modification

Events with an outcome of treatment modification (i.e. treatment interruption, treatment delay, or dose reduction) are summarised in Table 42. This table includes any AE with an outcome of treatment interruption, treatment delay, or dose reduction (whether or not the AE caused the modification). Treatment modification due to AEs tended to occur more frequently during TAS-102 treatment (58.2%) compared to placebo treatment (22.0%) in the TAGS study. Neutropenia (25.7%) and anaemia (8.8%) were the most frequently reported AEs leading to treatment modification. AEs leading to treatment modification (interruption, delay, or dose reduction) were mostly either myelosuppressive or gastrointestinal in nature, or related to underlying disease.

A total of 36 patients in the TAS-102 arm (10.7%) and 2 patients in the placebo arm (1.2%) experienced AEs with an outcome of dose reduction. The two most common events leading to dose reduction in the TAS-102 arm of TAGS were neutropenia (3.6%; n=12) and anaemia (2.1%; n=7). Events of febrile neutropenia, pancytopenia, diarrhoea, and neutrophil count decreased each had an outcome of dose reduction for a total of 3 patients (0.9%); no other individual preferred term had an outcome of dose reduction for more than 2 patients (0.6%).

Table 42. Summary of events with an outcome of treatment modification, incidence ≥1% in the TAS-102 arm of TAGS and RECOURSE (AT population)

	TAGS (mGC)		RECOURSE (mCRC)	
Preferred Term, %	**TAS-102 N = 335**	**Placebo N = 168**	**TAS-102 N = 533**	**Placebo N = 265**
All events with outcome treatment modification[a]	**58.2**	**22.0**	**54.2**	**13.6**
Neutropenia	25.7	0	19.9	0
Anaemia	8.7	1.8	5.4	0.8
Leukopenia	4.8	0	0.9	0
Nausea	4.5	2.4	1.9	0.4
Fatigue	3.9	1.8	3.0	0.4
Vomiting	3.3	0.6	1.9	0
Thrombocytopenia	2.4	0	0.6	0
Abdominal Pain	2.1	0.6	1.1	0.8
Decreased Appetite	2.1	1.8	1.7	1.9
Diarrhoea	2.1	0.6	2.4	0
Asthenia	1.8	1.2	1.3	0.8
Pancytopenia	1.5	0	0.2	0
Pyrexia	1.5	0.6	2.8	1.1
Blood Bilirubin Increased	1.2	0.6	0.9	0.4
Dysphagia	1.2	0.6	0	0
Gastrointestinal Haemorrhage	1.2	0.6	0	0
Platelet Count Decreased	1.2	0	1.3	0
White Blood Cell Count Decreased	1.2	0	1.5	0

Abbreviations: AT = as treated; Gr = Grade; mCRC = metastatic colorectal cancer; mGC = metastatic gastric cancer; N = number of patients in arm; n = number of patients in group

[a] Includes any AE with an outcome of treatment interruption, treatment delay, or dose reduction.

Occurrence of AEs with an outcome of treatment modification for both treatment groups tended to be higher in the TAGS study compared to the RECOURSE study. However, the difference in occurrence of AEs tended to be smaller in the TAGS study (36.0%) compared to the RECOURSE study (40.6%).

Post-marketing experience

From post-marketing experience, myelosuppressive (anaemia, neutropenia, leukopenia, thrombocytopenia and febrile neutropenia) events, gastrointestinal events (nausea, vomiting and diarrhoea) and infections remain the primary safety concerns with Lonsurf according to post-marketing experience of Lonsurf for mCRC.

2.5.1. Discussion on clinical safety

As a result of the eligibility criteria for the TAGS study, all patients in the safety population had an ECOG PS of 0 or 1, as well as normal or mildly abnormal haematological parameters. The to-be-treated patient population in clinical practice is expected to include more frail patients with e.g. ECOG PS of 2 and/or more

impaired renal function. Currently available study data on the effects of TAS-102 do not allow a proper characterisation of the safety profile of TAS-102 in a more frail population with mGC. However, in the TAGS study, the overall incidence of TEAEs did not increase with advancing levels of renal or hepatic impairment. Moreover, in a Japanese post-marketing surveillance study with respect to TAS-102 treatment for mCRC the incidence of any grade and grade ≥3 adverse reactions in patients with a baseline ECOG PS 2 was similar to the incidence of respective adverse reactions in patients with an ECOG PS of 0 or 1. Aforementioned data allow safe use of TAS-102 in more frail patients with mGC in clinical practice.

Regarding patient exposure, the median duration of therapy was rather short but longer in the TAS-102 treatment group (median 6.7 weeks) compared to the placebo treatment group (median 5.7 weeks). The most important reason for premature treatment discontinuation was progression of disease (>70% of patients in both treatment groups). The rather short duration of therapy prevents assessment of long-term safety, but this is in accordance with the observed relatively short PFS in this disease setting. The patients in the TAS-102 arm in TAGS had a similar exposure to TAS-102 when compared to the patients in the TAS-102 arm in RECOURSE.

Most patients experienced at least one TEAE of any Grade in the TAGS study, and the majority experienced Grade ≥3 events. Severe, life-threatening, disabling or fatal AEs (i.e. Grade ≥3 AEs) and treatment-related AEs tended to be reported more frequently in the TAS-102 treatment group than in the placebo treatment group. This also applies to the occurrence of treatment-related SAEs.
The pattern of TEAEs in general and treatment-related emergent (serious) AEs in the TAGS study is comparable to that observed in the previous placebo-controlled RECOURSE study on the effects of TAS-102 in mCRC. However, incidence of Grade ≥3 AEs (79.7% vs. 69.4%), SAEs (42.7% vs. 29.6%), AEs with outcome dose modification (58.2% vs. 54.2%), and AEs with outcome death (13.4% vs. 3.2%) tended to occur more frequently upon TAS-102 treatment in respectively the TAGS study compared to the RECOURSE study. Observed differences between TAS-102 and placebo for respective outcomes were not consistently larger in the TAGS study than in the RECOURSE study. This finding indicates that the higher incidence of AEs in the TAGS study as compared to the RECOURSE study is probably due to other factors than TAS-102 treatment itself. It is agreed with the applicant that the higher incidence of (serious) AEs in the TAGS study as compared to the RECOURSE study may be explained by the fact that the mGC patients tend to be frailer, sicker and have poorer prognosis than patients with mCRC.

Among the most frequently reported events (occurrence ≥10%), the largest differences between arms were observed for myelosuppressive AEs (specifically: neutropenia / neutrophil count decreased, anaemia, and leukopenia). For some gastrointestinal disorders including nausea, vomiting, and diarrhoea, and fatigue modest differences were observed between study arms (with higher incidence in the TAS-102 arm). Aforementioned AEs tended to be reported more frequently in patients treated with TAS-102 in the TAGS study compared to the RECOURSE study.

Treatment-related AEs tended to be reported more frequently in TAS-102 treated patients compared to placebo-treated study patients. Treatment-related AEs tended to occur less frequently in study patients treated with TAS-102 in the TAGS study compared to study patients treated with TAS-102 in the RECOURSE study, with the exception of leukopenia, thrombocytopenia, and lymphopenia.

Occurrence of death on treatment or within 30 days after the last treatment dose tended to be lower for TAS-102 treatment (18.4%) compared to placebo treatment (24.7%). It is difficult to determine the cause of death in patients with mGC in a poor condition due to previous treatment for this condition, comorbidities, and concomitant medication. Despite these limitations, disease progression appears to be the main cause of death in both patient groups. According to the investigators, no deaths due to AEs related to TAS-102 treatment were observed in the TAGS study.

Occurrence of AEs with outcome death was similar in study patients treated with TAS-102 (13.4%) and placebo (11.3%). This is remarkable considering the more extensive patient exposure for TAS-102 compared to placebo treatment. The most common AE with an outcome of death in both treatment groups was general physical health deterioration. There were 3 patients experiencing pulmonary embolism with an

outcome of death in the TAS-102 arm vs. 0 in the placebo arm, considered not related to study treatment; and 3 different patients experienced septic shock with an outcome of death in the TAS-102 arm vs. 0 in the placebo arm. Only in 1 case of septic shock, the applicant assessed that a causal role of TAS-102 for the event cannot be excluded, whereas the investigator did not consider the event as related to study medication. Though deaths due to pulmonary embolism or septic shock were (in most cases) not identified as ADRs in the TAGS study, it is noted that both AEs are listed as ADRs in the SmPC of Lonsurf. A contribution of TAS-102 to these events cannot be ruled out, but it is difficult to definitively conclude on this with the limited data available. In any case, it is indicated for both pulmonary embolism and septic shock in SmPC section 4.8 that fatal cases have been reported.

The occurrence of AEs with outcome death upon TAS-102 treatment tended to be higher in the TAGS study (13.4%) compared to the RECOURSE study (3.2%). According to the applicant, the difference in the number of AEs with outcome of death between TAGS and RECOURSE is probably due to the different patient populations and the increased morbidity of the patients in TAGS. In support of this, OS of TAS-102 treated patients with mGC in the TAGS study tends to be lower compared to TAS-102 treated patients with mCRC in the RECOURSE study (mOS 5.7 vs. 7.1 months; Lonsurf mCRC EPAR).

The incidence of SAEs was similar between the TAS-102 and placebo arms in the TAGS study (42.7 vs. 41.7%). However, treatment-related SAEs tended to be reported more often in study patients treated with TAS-102 (11.6%) compared to those treated with placebo (3.6%).
The most common SAE in both arms was general physical health deterioration, generally secondary to progression of disease. SAEs at an incidence of >1% in the TAS-102 treatment group that were reported more than 1% more frequently in the TAS-102 treatment group compared to the placebo treatment group in the TAGS study were anaemia, pancytopenia, (febrile) neutropenia, neutropenic sepsis, vomiting, and diarrhoea, i.e. myelosuppressive and gastro-intestinal AEs. Similar trends for SAEs either or not treatment-related were observed in the RECOURSE study.

AEs of special interest included myelosuppressive and gastro-intestinal AEs. Overall incidence of AEs in the blood and lymphatic SOC tended to be higher in the TAS-102 arm (63.6%) than in the placebo arm (25%) in the TAGS study. Haematologic AEs / laboratory abnormalities were generally manageable when they occurred.
In the SOC infections and infestations the absolute incidence of events of this type included related events was higher in the TAS-102 arm than in the placebo arm. However, occurrence of serious and severe (Grade $\geqslant$3) AEs, and AEs with an outcome of treatment discontinuation in this SOC were comparable. The overall incidence of events with an outcome of death was low in both arms, and the difference between arms was <1%. Reported AE rates with respect to myelosuppressive AEs tended to be lower in the TAGS study compared to the RECOURSE study. Hence, no new safety concerns with respect to infections and infestations emerged from the TAGS study.

The overall incidence of events in the SOC of gastrointestinal disorders tended to be slightly higher in the TAS-102 group than in the placebo arm of TAGS (72.8% vs. 67.3%). Occurrence of serious and severe (Grade ≥3) events was not higher in the TAS-102 arm compared to the placebo arm.
A total of 54.9% of patients in the TAS-102 arm and 45.8% of patients in the control arm reported nausea, diarrhoea, and/or vomiting. Occurrence of Grade ≥3 AEs was similar. Incidence of nausea, vomiting, or diarrhoea with an outcome of treatment discontinuation was similar between arms. Overall, increases in the occurrence of diarrhoea, nausea, and vomiting in the TAS-102 arm in comparison to placebo arm is less pronounced compared to what was observed in previous RECOURSE study. Hence, no new safety concerns with respect to gastrointestinal disorders emerged from the TAGS study.

AEs related to liver impairment were reported at similar rates upon TAS-102 and placebo treatment in the TAGS study.

Occurrence of AEs in both treatment groups varied among different levels of renal impairment. Consistent trends in the occurrence of AEs in patients with normal renal function, mild renal impairment and moderate renal impairment were however not observed for TAS-102 and placebo treatment in the TAGS study in mGC.

In pooled safety data of the TAGS and RECOURSE study overall incidence of AEs upon TAS-102 treatment was similar for patients with normal renal function, mild and moderate renal impairment. However, the incidence of serious, severe treatment-emergent AEs and AEs leading to dose modification upon TAS-102 treatment tended to be higher in patients with moderate renal impairment compared to those without or mild renal impairment (defined as a difference of at least 5%). This information is reflected in section 4.4 of the SmPC.

Reported haematologic laboratory abnormalities were neutropenia, anaemia, leukopenia, lymphopenia, and thrombocytopenia. Overall, severe (4.3 - 26.8% vs. 7.4 – 8%) and potentially life-threatening (0 – 11.3% vs. 0%) haematologic laboratory abnormalities tended to occur more frequently during TAS-102 treatment compared to placebo treatment. Differences in occurrence were largest for neutropenia, leukopenia, and anaemia.

With respect to chemistry laboratory abnormalities, there were no notable differences between TAS-102 and placebo arms for most parameters. However, the incidence of Grade 3 or 4 hypokalaemia that worsened from baseline was higher in the TAS-102 arm (2.4%) than in the placebo arm (0.6%). This observation may be due to the higher incidence of gastrointestinal effects (e.g. diarrhoea, vomiting) observed with TAS-102 treatment compared to placebo treatment. For example, Grade ≥3 diarrhoea and vomiting were more frequently observed in the TAS-102 arm (2.7% and 3.6%, respectively) than the placebo arm (1.8% and 1.8%, respectively). The SmPC already includes a warning for clinical monitoring of gastrointestinal events and management as clinically indicated.
In addition, hepatobiliary abnormalities were commonly reported and were more frequently observed in the TAS-102 arm vs. the placebo arm, in particular elevations of bilirubin and alkaline phosphatase. In the TAS-102 arm 2 patients met the laboratory criteria for Hy's Law. The applicant acknowledged the absolute high incidence of hepatobiliary laboratory abnormalities reported in Lonsurf arm, in particular bilirubin and alkaline phosphatase, but pointed out that when comparing these incidences to the placebo arm, the difference is <5%. It is agreed with the applicant that there is no need for additional precautionary statements with recommendations for monitoring of these events during treatment in the SmPC.

No clinically relevant mean or median changes in body weight or vital signs were observed in either study treatment group. Median changes from baseline at the end of each cycle were relatively stable in both treatment groups over the first several treatment cycles.

Though occurrence of AEs was higher among study patients treated with TAS-102 compared to those treated with placebo in the TAGS study, occurrence of AEs during TAS-102 treatment was overall comparable for patients of different age and race.

Patients with an ECOG PS of 0 at baseline generally had lower rates of adverse events than patients with a score of 1, with the exception of AEs of special interest in the TAS-102 group (ECOG 0: 76.4%; ECOG 1: 68.4%). The applicant additionally presented a comparative analysis (ECOG PS 1 vs. ECOG PS 0, and vs. placebo) of the frequency of overall AEs, treatment related AEs, SAEs, AEs leading to discontinuation and leading to death. This analysis did show that the absolute values of serious, severe AEs and AEs leading to death in the ECOG 1 subgroup were higher than in the ECOG 0 subgroup in the TAS-102 arm. When comparing the relative values vs. placebo of these events however, the differences appear similar or even lower in the ECOG 1 subgroup as compared to the ECOG 0 subgroup.
Occurrence of AEs during TAS-102 treatment was overall comparable for patients of different race. Also, occurrence of TEAEs in Asian patients and patients from Japan in the TAGS and RECOURSE study was similar with respect to TAS-102 treatment (Asian patients: 100% vs. 99.5%; Japanese patients: 100% vs. 99.4%) but tended to be lower during placebo treatment in the TAGS study compared to the RECOURSE study (Asian patients: 82.8 vs. 92.6%; Japanese patients: 81.5 vs. 92.0%).

Two patients (0.6%) mistakenly received a single overdose of TAS-102 in the TAGS study. No fatal AEs occurred upon respective accidental overdoses.

AEs with an outcome of treatment discontinuation tended to be observed less frequently in the TAS-102 arm (12.8%) compared to the placebo arm (16.7%). Events with an outcome of discontinuation were most common in the SOCs of gastrointestinal disorders and general disorders and administration site conditions.

Treatment modification tended to occur more frequently during TAS-102 treatment (58.2%) compared to placebo treatment (22.0%) in the TAGS study. AEs leading to treatment modification (interruption, delay, or dose reduction) were mostly either myelosuppressive or gastrointestinal in nature, or related to underlying disease and were generally comparable with observations from RECOURSE, i.e. the established safety profile of TAS-102.

Observed post-marketing safety data are consistent with the current SmPC. At this time, there are no additional safety signals.

2.5.2. Conclusions on clinical safety

The safety profile of TAS-102 in the TAGS study in mGC is overall similar to that of TAS-102 in previous RECOURSE study in mCRC. No new safety signals emerged. TAS-102 was generally well tolerated and the identified risks are considered manageable in clinical practice. Most frequently reported TEAEs were myelosuppressive (e.g. neutropenia, anaemia, leukopenia) or gastrointestinal (e.g. nausea, decreased appetite, diarrhoea) by nature, for which close monitoring is already recommended in the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 7.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Bone marrow suppression Gastrointestinal symptoms (nausea, vomiting and diarrhoea) Infection Use in patients with moderate renal impairment
Important potential risks	Developmental toxicity/Use in pregnant and breast-feeding women

Missing information	Use in patients with severe renal impairment Use in patients with cardiac disorders Use in patients in worse condition than ECOG 0-1.

No changes to the list of safety concerns were made as a result of the new indication (metastatic gastric cancer).

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
TO-TAS-102-107- A phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of trifluridine-tipiracil in patients with advanced solid tumours and varying degrees of renal impairment. On-going	Compare PK profile and assess safety and tolerability of trifluridine-tipiracil in patients with advanced solid tumours (except breast cancer) and varying degrees of renal impairment.	Use in patients with severe renal impairment	Final report	June 2019
DIM-95005-001 (PROMETCO) - A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective On-going	Provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions.	Use in patients in a worse condition than ECOG 0-1	Final report	March 2023

The study DIM-95005-001 (PROMETCO), a non-interventional real world data study, as an additional pharmacovigilance activity (category 3 study) was added to the pharmacovigilance plan in order to further characterise the missing information "Use in patients in worse condition than ECOG 0-1".

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Bone marrow suppression	Routine risk minimisation measures: SmPC sections 4.2 and 4.8 SmPC section 4.4 where advice is given on monitoring blood cells count. PL sections 2 and 4 Legal status Labelling Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Gastrointestinal symptoms (nausea, vomiting and diarrhoea)	Routine risk minimisation measures: SmPC section 4.8 SmPC section 4.4 where advice is given on monitoring the occurrence of gastrointestinal symptoms. PL sections 2 and 4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Infection	Routine risk minimisation measures: SmPC sections 4.2 and 4.8 SmPC section 4.4 where advice is given on monitoring the patient's condition. PL sections 2 and 4 Legal status Additional risk minimisation	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	measures: None	
Use in patients with moderate renal impairment.	Routine risk minimisation measures: SmPC sections 4.2 , 4.4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: TO-TAS-102-107 clinical study
Developmental toxicity/Use in pregnant and breast feeding women	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC section 4.4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: TO-TAS-102-107 study
Use in patients with cardiac disorders	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients in a worse condition than ECOG 0-1	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Study DIM-95005-001 (PROMETCO)

No changes to the risk minimisation measures were made as a result of the new indication (metastatic gastric cancer). Routine risk minimisation measures remain sufficient to manage the risks of Lonsurf.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a (full) user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the proposed changes introduced in the Package Leaflet (PL) as part of this variation application, are limited to:

- the addition of the new indication for mGC (including adenocarcinoma of the gastroesophageal junction) in section 1. Patient friendly terms used to describe the new indication are already present in the PL of another approved product in the same indication and;
- the deletion or moving of some terms in the section 4.

It is agreed that the changes introduced by this variation do not substantially impact the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication for Lonsurf in this procedure is: "Lonsurf is indicated as 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".

3.1.2. Available therapies and unmet medical need

For advanced/metastatic GC in third- or later-line treatment, there are neither approved nor standard therapies. Nevertheless, selected patients could be offered chemotherapy without proof of OS benefit. Then again, the ESMO guidelines note on this matter that second-line treatment options may be used sequentially in second and third line, but indicates caution that "there is no clear evidence for a benefit beyond second-line treatment" (Smyth, 2016).

3.1.3. Main clinical studies

The single pivotal study in this procedure is TAGS, a randomised, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC vs. placebo plus BSC in patients with mGC refractory to standard treatments, i.e. patients who had received ≥2 prior regimens for advanced disease and were refractory to or unable to tolerate their last prior therapy. Importantly, these prior regimens were required to have included a fluoropyrimidine-, platinum-, and either a taxane- and/or irinotecan-containing regimen (plus patients with HER2+ tumours were required to have received prior anti-HER2 therapy). OS was the primary endpoint of this study, PFS was the key secondary efficacy endpoint, and ORR and DCR were among the other secondary endpoints. In total, 507 patients were randomized 2:1 to either TAS-102 (N=337) or placebo (N=170).

3.2. Favourable effects

On OS, the effect of TAS-102 relative to placebo resulted in a HR of 0.69 (95% CI: 0.560, 0.855,; p=0.0003), with mOS of 5.7 months for TAS-102 versus 3.6 months for placebo, reflecting an increase in mOS of 2.1 months. The results of all sensitivity analyses were consistent with this primary analysis of OS. In the subgroup analyses the OS HRs in general favoured the TAS-102 group.

The results for all secondary (efficacy) endpoints are in line with the OS data.

For the key secondary endpoint PFS, a statistically significant benefit was also shown. Treatment with TAS-102 when compared to placebo resulted in a HR of 0.57 (95% CI: 0.467, 0.701; p<0.0001), with mPFS of 2.0 months for TAS-102 versus 1.8 months for placebo, reflecting an increase in mPFS of 0.2 months. The results of all relevant sensitivity analyses were consistent with this primary analysis of PFS. The PFS HRs favoured the TAS-102 group across all subgroups examined.

The ORR was numerically higher for the TAS-102 arm when compared to the placebo arm (4.5% vs. 2.1%, respectively; Δ +2.4% [95% CI: -0.9, 5.7]; p=0.2833).

A statistically significant improvement was observed in the DCR for the TAS-102 arm when compared to the placebo arm (44.1% vs. 14.5%, respectively; Δ +29.7% [95% CI: 21.6, 37.7], p<0.0001).

Treatment with TAS-102 resulted in a statistically significant reduction in the rate of deterioration to ECOG PS ≥2 compared to placebo. The median time to ECOG PS ≥2 was 4.3 months (95% CI: 3.7, 4.7) in the TAS-102 arm vs. 2.3 months (95% CI: 2.0, 2.8) in the placebo arm (HR=0.69; 95% CI: 0.562, 0.854; p=0.0005).

QoL as assessed using the EORTC QLQ-C30 and QLQ-STO22, was balanced between both treatments arms at baseline, and there were no (mean/median) changes ≥10 points in overall QoL from baseline up to cycle 3 in either treatment group. Treatment with TAS-102 resulted in a numerically longer median time to deterioration by ≥5 points in global health status using the above-mentioned QoL questionnaires compared to placebo. The median time to deterioration was 2.6 months (95% CI: 2.3, 3.3) in the TAS-102 arm vs. 2.3 months (95% CI: 1.4, NA) in the placebo arm (HR=1.27; 95% CI: 0.854, 1.875; p=0.2350).

3.3. Uncertainties and limitations about favourable effects

The efficacy of TAS-102 in mGC patients with an ECOG PS score >1 is not known, as these patients were excluded from TAGS (which is adequately reflected in section 5.1 of the proposed amended SmPC).

The clinical relevance of the observed 0.2-month improvement in mPFS (i.e. approximately 6 days) is uncertain.

The MAH was not able to confirm that the QoL questionnaires were completed at the beginning of each visit, prior to *any* clinical activities (i.e. before any extensive contact and consultation with study site personnel). As a result, the patient responses may have been biased, as e.g. medical information could bias retrospective evaluation. Also, there were a lot of missing data at later time-points. Therefore, no conclusions can be drawn on the basis of the QoL data submitted and these data have not been included in the SmPC.

3.4. Unfavourable effects

The incidence of AEs in the different AE categories for TAS-102 vs. placebo were any AE: 97.3% vs. 93.5%; any treatment-related AE: 80.9% vs. 56.6%; Grade ≥3 AEs: 79.7% vs. 57.7%; SAEs: 42.7% vs. 41.7%; treatment-related SAEs: 11.6% vs. 3.6%; discontinuation due to an AE: 12.8% vs. 16.7%; dose modification due to an AE: 58.2% vs. 22.0%; death due to an AE: 13.4% vs. 11.3%.

104 Study patients died while on study treatment or within 30 days after the last dose of study treatment. Most patients died due to disease progression (TAS-102 13.9% vs. placebo 23.5%). The proportion of patients who died due to an AE tended to be higher for TAS-102 (4.2%) than for placebo treatment (1.2%). However, according to the investigators none of the TAS-102-treated study patients died due to a treatment-related AE.

Occurrence of liver impairment-related AEs was similar for TAS-102 (7.5%) and placebo treatment (6.0%). The same applies to the occurrence of renal impairment-related AEs in these treatment groups (TAS-102: 5.4%, placebo: 6.0%).

In general, serum chemistry abnormalities occurred at similar frequencies during TAS-102 and placebo treatment. However, the incidence of Grade 3 or 4 hypokalaemia that worsened from baseline was higher in the TAS-102 arm (2.4%) than in the placebo arm (0.6%). Also, hepatobiliary abnormalities were more frequent in the TAS-102 arm, in particular bilirubin elevations of 1.5 x ULN were reported for 14.9% vs. 11.9% in the control arm, and elevations of 2 x ULN reported for 11.6% vs. 7.1% for the control arm; elevation of alkaline phosphatase of 1.5 x ULN was reported for 45.1% of the TAS-102 arm and 41.7% of the control arm. In the TAS-102 arm, 2 patients met the laboratory criteria for Hy's Law.

A total of 43 patients in the TAS-102 arm (12.8%) and 28 patients in the placebo arm (16.7%) experienced 1 or more AEs with an outcome of treatment discontinuation. Events with an outcome of discontinuation were most common in the SOCs of gastrointestinal disorders (4.5% [TAS-102 arm] vs. 6.5% [placebo arm]) and general disorders and administration site conditions (2.4% vs. 6.0%).

Treatment modification due to AEs tended to occur more frequently during TAS-102 treatment (58.2%) compared to placebo treatment (22.0%) in the TAGS study. AEs leading to treatment modification (interruption, delay, or dose reduction) were mostly either myelosuppressive or gastrointestinal in nature, or related to underlying disease.

In conclusion, the safety profile of TAS-102 in the TAGS study in mGC is overall similar to that of TAS-102 in previous RECOURSE study in mCRC. No new safety signals emerged. TAS-102 was generally well tolerated and the identified risks (see RMP) are considered manageable in clinical practice. Most frequently reported TEAEs were myelosuppressive (e.g. neutropenia, anaemia, leukopenia) or gastrointestinal (e.g. nausea, decreased appetite, diarrhoea) by nature, for which close monitoring is already recommended in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

As a result of the eligibility criteria for the TAGS study, all patients in the safety population had an ECOG PS of 0 or 1, as well as normal or mildly abnormal haematological parameters and liver function tests. The

to-be-treated patient population in clinical practice is expected to include more frail patients with e.g. ECOG PS of 2 and/or more impaired renal function. Currently available study data on the effects of TAS-102 therefore do not allow a proper characterization of the safety profile of TAS-102 in more frail subpopulations with mGC. However, limitations with respect to particular subpopulations are appropriately reflected in the SmPC.

Occurrence of TEAEs in Asian patients and patients from Japan in the TAGS and RECOURSE study was similar with respect to TAS-102 treatment (Asian patients: 100% vs. 99.5%; Japanese patients: 100% vs. 99.4%) but tended to be lower during placebo treatment in the TAGS study compared to the RECOURSE study (Asian patients: 82.8 vs. 92.6%; Japanese patients: 81.5 vs. 92.0%). Since differences in occurrence of AEs in the TAGS and RECOURSE study were only observed for placebo treatment but not for active TAS-102 treatment, this issue is not further pursued.

3.6. Effects Table

Table 43. Effects table for Lonsurf (TAS-102) as 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 systemic treatment regimens for advanced disease (data cut-off for OS data: 27-Mar-2018; for all other [non-OS] clinical data: 31-Mar-2018)

Effect	Short description	Unit	TAS-102	Placebo	Uncertainties / Strength of evidence	References
Favourable effects						
OS	Median time from date of randomization to date of death due to any cause	Months	5.7	3.6	HR=0.69 (95% CI: 0.560, 0.855) p=0.0003 Clinically relevant	Section **2.4.2. Main study** and **2.4.3. Discussion on clinical efficacy**
Unfavourable effects						
Grade ≥3 TEAEs	Patients with ≥1 treatment-emergent adverse event Grade ≥3	%	79.7	57.7		
Treatment-related SAEs	Patients with ≥1 treatment-related serious adverse event	%	11.6	3.6		
Anaemia	Grade ≥3	%	18.8	7.7		
Neutropenia + neutrophil count decreased	Grade ≥3	%	34.6	0		
Nausea	Grade ≥3	%	3.0	3.0		
Decreased appetite	Grade ≥3	%	8.7	6.5		
Diarrhoea	Grade ≥3	%	2.7	1.8		

Abbreviations; AEs = adverse events; CI = confidence interval; DCR = disease control rate; ECOG PS = Eastern cooperative oncology group performance score; EORTC = European organisation for research and treatment of cancer ; HR = ; ORR = OS = overall survival; PFS = progression-free survival; QLQ-C30 = QoL questionnaire - core 30; QLQ-STO22 = QoL questionnaire - gastric cancer-specific module; QoL = quality of life; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The prognosis of patients with mGC overall is poor, but even more so in the third- and later-line treatment setting, as shown by the ≤6-month mOS observed in several recent studies. In this disease setting, there are neither approved nor standard therapies and thus new treatment options are necessary.

The OS benefit observed for TAS-102 of 2.1 months in TAGS was statistically significant and clinically relevant. Moreover, the OS result was robust and supported by the key secondary efficacy endpoint PFS and most other secondary efficacy endpoints (e.g. DCR). Therefore, in spite of this being an application based on a single pivotal study, the efficacy results are considered quite convincing.

There were no unexpected findings in the assessment of TEAEs in the safety population, with the known myelosuppressive AEs (e.g. neutropenia, leukopenia, anaemia, and thrombocytopenia) and gastro-intestinal AEs (e.g. diarrhoea, nausea, vomiting), and fatigue. TAS-102 was generally well tolerated and the identified risks (see RMP) are considered manageable in clinical practice. When compared with the known safety profile of TAS-102 for the mCRC patient population, no new safety signals were identified.

Only study patients with a relatively good ECOG PS and normal or only mildly abnormal haematological and chemistry parameters were included in the TAGS study. Currently available study data on the effects of TAS-102 therefore do not allow a proper characterisation of the safety profile of TAS-102 in more frail subpopulations with mGC. However, limitations with respect to particular subpopulations are adequately reflected in the SmPC.

3.7.2. Balance of benefits and risks

Treatment with TAS-102 resulted in a clear OS benefit in a disease setting with a very poor prognosis, and wherein there are neither approved nor standard therapies.

The overall safety profile of TAS-102 in patients with mGC appears to be similar to that observed for TAS-102 in patients with mCRC, and is considered acceptable in this disease setting.

The benefit-risk balance is therefore considered positive in the target population as represented by the above mentioned indication.

3.7.3. Additional considerations on the benefit-risk balance

The final proposed indication is:

*Lonsurf is indicated **as 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 (see section 5.1)**~~or are not considered candidates for, available therapies including fluoropyrimidine-, platinum-, and either a taxane- or irinotecan-based chemotherapy.~~*

For brevity reasons the previous regimen followed by patients have been reflected in a more general way making then clear specification on them in section 5.1

3.8. Conclusions

The B/R of Lonsurf (trifluridine/tipiracil) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment, as monotherapy, of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two systemic treatment regimens for advanced disease for Lonsurf; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 7.0 has also been submitted and updated in accordance with Template Rev 2. For clarification, the term monotherapy has also been added to the existing indication in metastatic colorectal cancer.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment, as monotherapy, of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two systemic treatment regimens for advanced disease for Lonsurf; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 7.0 has also been submitted and updated in accordance with Template Rev 2. For clarification, the term monotherapy has also been added to the existing indication in metastatic colorectal cancer.

Summary

Please refer to the published Assessment Report Lonsurf H-3897-II-0012.

Attachments

1. Product information (changes highlighted) of Lonsurf as adopted by the CHMP on 25 Juy 2019.

Appendix

1. CHMP AR on additional 1 year of marketing exclusivity

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification within 15 days of receipt of the opinion documents. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/principles-be-applied-deletion-commercially-confidential-information-disclosure-emea-documents_en.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first.