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EMA/CHMP/641866/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Teysuno

International non-proprietary name: TEGAFUR / GIMERACIL / OTERACIL

Procedure No. EMEA/H/C/001242/II/0018

Note

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

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List of abbreviations

AEGC	Advanced esophagogastric cancer
EOX	Epirubicin + oxaliplatin + capecitabine
EOS	Epirubicin + oxaliplatin + S-1
EU	European
FAM	5-FU + doxorubicin + mitomycin C
FAMTX	5-FU + doxorubicin + methotrexate
FT	Tegafur; 5-fluoro-1-(tetrahydro-2-furyl)uracil
GT	Glutamyl-transpeptidase (glutamyltranspherase)
GCP	Good Clinical Practices
GI	Gastrointestinal
ICH	International Conference on Harmonization
IV	Intravenous or Intravenously
LVEF	Left Ventricular Ejection Fraction
L	Liter
LLN	Lower Limit of Normal
µmol	Micromole
m2	Meters squared
MCF	Mitomycin C + cisplatin + 5-FU
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NE	Not Evaluable
Ng	Nanogram
ORR	Overall Response Rate
OS	Overall Survival
Oxo	Oteracil potassium; monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
S-1	Teysuno; an oral pyrimidine fluoride-derived anticancer agent. Consists of tegafur combined with gimeracil and oteracil.
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
TOI	Taiho Oncology, Inc.
UBC	United BioSource Corporation
ULN	Upper Limit of Normal
US/USA	United States/United States of America
WBC	White Blood Cell
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 for single variation of Commission Regulation (EC) No 1234/2008, the MAH submitted to the European Medicines Agency an application for a variation including an extension of indication, following a work sharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name :
Teysuno	Tegafur, Gimeracil, Oteracil

The following variation was requested:

Variationrequested		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for a modification of the already approved wording of indication from:

“Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with **cisplatin** (see section 5.1)” to:

“Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in combination with **a platinum- based regimen** (see section 5.1)”.

All the other sections of the SmPC have been modified accordingly.

The recommended dose of S-1 in combination with Cisplatin (75 mg/m2, day 1) is 25 mg/m2 (expressed as tegafur content) twice daily, morning and evening, for 21 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.

The recommended dose of S-1 in combination with Oxaliplatin (130 mg/m2, day 1) (with or without other agents like epirubicin) is 25 mg/m2 (expressed as tegafur content) twice daily, morning and evening, for 14 consecutive days followed by 7 days rest (1 treatment cycle). This treatment cycle is repeated every 3 weeks.
In a triplet regimen with S-1, oxaliplatin and epirubicin, the recommended dose of epirubicin is 50 g/m2 once every 3 weeks.

Scientific advice

No Scientific advice has been sought by the MAH regarding this type II variation.

2. Scientific discussion

2.1. Introduction

Problem statement

Gastric cancer is the second leading cause of cancer mortality in the world (Wagner, 2006). The majority of cases are diagnosed at a late stage, moreover, in the majority of patients who undergoes surgery, disease eventually recurs. In patients with recurrent locally advanced or metastatic disease, the only available treatment option consists of palliative chemotherapy, with very limited effect reported in the literature to date in terms of prolongation of overall survival and symptoms palliation. Current treatment guidelines in the European Union (EU) and United States for metastatic or locally advanced disease recommend, in patients with HER2 negative status, two drug combinations due to increased toxicity associated with three drug regimens (Waddell, 2013; NCCN, 2013). Recommended options for first-line treatment include a fluoropyrimidine (5-fluorouracil or capecitabine) and a platinum agent (cisplatin or oxaliplatin) with an anthracycline (epirubicin), topoisomerase inhibitor (irinotecan), or taxane (docetaxel) added as the third agent in the combination for medically fit patients with relatively good performance status (NCCN, 2013; Waddell, 2013).

In recent years, substitution of cisplatin with oxaliplatin, in patients with a contraindication for cisplatin, has been suggested in the literature on the basis of few reported studies and on a recent meta-analysis (Cunningham, 2008). However, Oxaliplatin is not currently registered for the treatment of patients with gastric carcinoma in EU. Oxaliplatin is a diaminocyclohexane-containing platinum compound with cytotoxic effects in a broad range of cancer cell types and in vivo tumour models (Raymond, 2002; Powles, 2007). It does not appear to be cross-resistant with cisplatin (Raymond, 2002; Culy, 2000). Like cisplatin, oxaliplatin acts by creating DNA lesions that prevent DNA replication and transcription. Differences in the number and type of DNA lesions caused by the two compounds and their effects on mRNA translation likely explain the reported differences in specificity and efficacy between them (Raymond, 2002; Becker, 2014). Oxaliplatin is approved for use in combination with fluoropyrimidines for adjuvant treatment of phase III colorectal cancer and first-line treatment of metastatic colorectal cancer in the Europe, US, and Asia (NCI, 2014; Mani, 2000).

Comparison of oxaliplatin and cisplatin in combination with fluoropyrimidines in advanced gastric cancer

Evidence from clinical trials supports the use of cisplatin plus 5-FU as standard first-line treatment for advanced HER 2 negative gastric cancer (Lordick, 2013; Montagnani, 2011). Substitution of 5-FU with oral fluoropyrimidines such as S-1 and capecitabine provides non-inferior efficacy. Several trials have been conducted to test the efficacy of substituting oxaliplatin to cisplatin in combination with fluoropyrimidines:

-A phase 2 European study that compared the combination of 5-FU and leucovorin plus oxaliplatin or cisplatin in 72 patients with advanced gastric cancer reported fewer grade 3/4 adverse events for patients who received oxaliplatin compared to patients who received cisplatin ($p<0.05$)(Popov, 2008). In addition, a median survival of 10 months for patients who received the oxaliplatin-based regimen versus 7 months for the cisplatin-based regimen was observed ($p=0.003$).

-A two-by-two trial design was used in the phase III Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial. A total of 1002 patients were randomized twice to receive either oxaliplatin or cisplatin and either capecitabine or 5-FU. All patients also received epirubicin. The four combinations were found to be equally effective (Cunningham, 2008).

-Another randomized, controlled, phase 3 trial conducted by the Arbeitsgemeinschaft Internistische Onkologie (AIO) in 220 patients with advanced gastric cancer compared treatment with 5-FU and leucovorin plus either cisplatin or oxaliplatin (Al-Batran, 2008). In a post-hoc analysis, elderly patients (≥ 65 years, n=94) who received oxaliplatin had a significantly better progression-free survival (6.0 vs 3.1 months; $p = 0.029$) than those who received cisplatin. Patients who received oxaliplatin-based treatment experienced less anaemia, alopecia, vomiting, nausea, fatigue, renal toxicity, and thromboembolism, but more peripheral neuropathy and elevations of the serum AST or ALT than those who received cisplatin treatment. The study was not powered to test overall survival, but survival was reported similar between the two groups (10.7 months oxaliplatin vs 8.8 months cisplatin) (Al-Batran, 2008).

-A meta-analysis of data from the phase 2 and phase 3 trials discussed above concluded that regimens containing oxaliplatin were associated with a moderately improved progression-free survival (HR 0.88; p = 0.02), and overall survival (HR 0.88; p = 0.04) compared to cisplatin in patients with advanced gastric cancer (Montagnani, 2011). Comparison of the toxicity showed that oxaliplatin was associated with less grade 3/4 neutropenia (OR = 0.53; p < 0.01), but more diarrhea (OR = 2.73, p < 0.01) and neurotoxicity (OR = 6.91; p < 0.01).

-A recent review concluded that oxaliplatin can substitute cisplatin in the treatment of gastric cancer due to the non-inferior efficacy and good tolerability of this agent in combination with fluoropyrimidines (Lordick, 2014).

About the product

S-1, also known as TS-1 or Teysuno, is an oral combination of three active substances, tegafur, gimeracil, and oteracil. After absorption, tegafur is converted by the liver into 5-fluorouracil (5-FU). Gimeracil is a dihydropyrimidine dehydrogenase (DPD) inhibitor that prevents degradation of 5-FU by the body and thus increases its availability. Oteracil decreases the breakdown of 5-FU into toxic metabolites in normal gastrointestinal mucosa and thus may reduce toxic side effects of the drug through inhibition of orotate phosphoribosyltransferase (OPRT) (Matt, 2011).

Approval of S-1 in combination with cisplatin in advanced gastric cancer patients in the EU was primarily based on results from the *First Line Advanced Gastric Cancer Study (FLAGS)* (Ajani, 2010). FLAGS was a phase 3, open-label, randomised, 2-arm study, conducted in 1053 patients at 147 sites in 24 countries in Europe, North America, Latin America, Australia, and Africa, tested the efficacy and safety of oral S-1 plus cisplatin compared to infusional 5-FU plus cisplatin in patients with advanced gastric cancer previously untreated with chemotherapy for advanced disease (Ajani, 2010). Patients were randomized to receive S-1 (25 mg/m2 twice per day for 21 days) plus cisplatin (75 mg/m2 i.v. on day 1 of 28 days) or infusional 5-FU (1000 mg/m2/24 hours as a 120-hour infusion) plus cisplatin (100 mg/m2 i.v. on day 1 of 28 days). The combination of S-1 plus cisplatin did not improve the primary endpoint of overall survival compared to 5-FU plus cisplatin (8.6 months S-1/cisplatin vs 7.9 months 5-FU/cisplatin, p=0.20). There were also no significant differences between the two treatments in terms of progression free survival (4.8 months S-1/cisplatin vs 5.5 months 5-FU/cisplatin, p=0.92), and response rates (29.1% S-1/cisplatin vs 31.9% 5-FU/cisplatin, p=0.4). Patients who received S-1/cisplatin had significantly reduced rates of grade 3/4 neutropenia (32.3% vs 63.6%), complicated neutropenia (5.0% vs 14.4%), stomatitis (1.3% vs 13.6%), and hypokalemia (3.6% vs 10.8%), and treatment-related death (2.5% vs 4.9%) (p<0.05), at least partly related to the lower cisplatin-dose administered in the S-1 arm. CHMP concluded that non-inferiority of S-1+ cisplatin vs 5FU+ cisplatin was demonstrated (European public assessment report, EMA).

In 2011, S-1, in combination with cisplatin (75 mg/m2 day 1), was approved in the EU for treatment of adults with advanced gastric cancer at a dose of 25 mg/m2 orally, twice per day for 21 days of a 4-week cycle.

2.2. Non-clinical aspects

Environmental Risk Assessment:

The applicant is asked to provide suitable information to verify that an increase in environmental exposure of the active ingredient is not to be expected. If acceptable information cannot be provided, the applicant is asked to submit an updated / revised environmental risk assessment according to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

2.3.2. Pharmacokinetics

S-1, also known as TS-1 or Teysuno, is an oral combination of three active substances, tegafur, gimeracil, and oteracil. After absorption, tegafur is converted by the liver into 5-fluorouracil (5-FU). Gimeracil and oteracil are included to reduce the metabolism of 5-FU thereby improving the bioavailability of 5-FU and reducing the toxic effects of its metabolites.

S-1 (25 mg/m^2) is currently approved for the treatment of advanced gastric cancer when given in combination with cisplatin (75 mg/m^2).

To support the inclusion of oxaliplatin (130 mg/m^2) as an alternative to cisplatin in combination with S-1 for treatment of patients with advanced gastric cancer, a summary of pharmacokinetic data were provided for S-1 in combination with oxaliplatin and bevacizumab in patients with advanced solid tumours (study TPU-S1109, Chung et al. 2011).

In this study, stage A was a 3-week cycle in which S-1 was started at 20 mg/m2 twice daily for 14 consecutive days, and escalated by 5 mg/m2, plus oxaliplatin (130 mg/m2) and bevacizumab (7.5 mg/kg IV) on day 1 of each 3-week cycle. Stage B was a 2-week cycle of S-1 administered at 25 mg/m2 twice daily for 7 consecutive days, and escalated by 5 mg/m2, plus oxaliplatin (85 mg/m2) and bevacizumab (5 mg/kg IV) on day 1 of each 2-week cycle. The MTD of S-1 in combination with a fixed dose of oxaliplatin and bevacizumab was determined to be 25 mg/m2 twice per day for 14 days of the 3-week cycle and 35 mg/m2 twice per day for 7 days of the 2- week cycle. According to the applicant, both regimens were safe and well-tolerated. PK measurements (Stage A only) revealed no PK interactions between S-1 components and oxaliplatin.

2.3.3. Pharmacodynamics

No data were submitted to support this application.

2.3.4. Discussion and conclusion on clinical pharmacology

To support the PK of the combination with oxaliplatin, the applicant submitted a summary of PK data for S-1 in combination with oxaliplatin and bevacizumab in patients with advanced solid tumours (study TPU-S1109). The study report, however, was not submitted (OC). The provided pharmacokinetic data indicated that there is no pharmacokinetic interaction between the S-1 components and oxaliplatin.

Not only is the applicant applying for inclusion of oxaliplatin as an alternative to cisplatin but implicitly also for carboplatin and for combination with oxaliplatin and other agents like epirubicin. The PK characteristics of the three platinum compounds are not identical and moreover the dosing regimen

(dose and frequency) is different. Therefore, the applicant is requested to submit data supporting the various combinations with S-1.

The platinum products currently available are cisplatin, oxaliplatin and carboplatin. The pharmacokinetic characteristics and mechanism of action of these three platinum compounds are not identical. Also the safety profile, and dosing regimen and scheme (every 2 weeks, every 3 weeks or every 4 weeks) is different for these compounds. Therefore, interchangeability of these platinum compounds should be substantiated by clinical efficacy and safety data.

2.4. Clinical efficacy

The data supporting the extension of indication of S-1 (Teysuno, TS1) in combination with **platinum-regimens** in patients with advanced gastric cancer is based on:

1- Regarding the combination Oxaliplatin-S1:

   a. the interim results of the phase 1, open-label dose-finding TPU-S1119 study where S-1 was administered in combination with oxaliplatin and epirubicin in patients with advanced solid tumours (Cohort 1 and 2) and in 7 patients with esophagogastric cancer (cohort 3) (table 1);

   b. the phase I TPU-S1109 trial, where patients with advanced solid tumours were treated in the USA with the combination S1-oxaliplatin-bevacizumab, in a 3-weekly (Stage A) and in a 2-weekly (Stage B) scheme (table 1);

   c. other studies reported in the literature have been mentioned as supportive, but in most of the cases they were conducted in non-Caucasian patients (table 2).

2- Regarding the combination Cisplatin-S1:

   a. The studies provided/assessed during the original MAA in EU of S-1 in combination with cisplatin in patients with advanced gastric cancer (table 3).

A description of the clinical studies included in the S-1 development program in support of the proposed extension of the indication is given in the following tables.

Table 1. Clinical development program of S-1 with Oxaliplatin in Caucasians

Study	Phase	Cohort	Dosages	Patients	Endpoints
TPU-S1119	1	Cohort 1 (solid tumors)	Oxaliplatin: 130 mg/m2 d1 Epirubicin: 50 mg/m2 d1 S-1:20 mg/m2 BID	6	**1°: MTD (DLT)** **2°: ORR**
		Cohort 2 (solid tumors)	Oxaliplatin: 130 mg/m2 d1 Epirubicin: 50 mg/m2 d1 S-1:25 mg/m2 BID	6	**1°: MTD (DLT)** **2°: ORR**
		Cohort 3 (AEGC)	Oxaliplatin: 130 mg/m2 d1 Epirubicin: 50	7	**1°: ORR**

			mg/m2 d1 S-1:25 mg/m2 BID		
TPU-S1109	1	Stage A (solid tumors)	S-1: 25 mg/m2 d1-14 Oxaliplatin: 130 mg/m2 d1 Bevacizumab 7.5 mg/kg d1 3 wk	23 (USA)	**1°: MTD (DLT)** **2°: ORR**
		Stage B (solid tumors)	S-1: 35 mg/m2 d1-7 Oxaliplatin: 85 mg/m2 d1 Bevacizumab 5mg/kg d1 2 wk	24 (USA)	**1°: MTD (DLT)** **2°: ORR**

BID: twice daily; AEGC: advanced esophagogastric cancer; ORR: overall response rate; ORR: Objective response rate; MTD: maximum Tolerated dose; DLT: dose limiting toxicity; USA: patients enrolled in the United States of America.

Table 2. Efficacy of S-1 plus oxaliplatin regimens – literature data

Study	Phase	Region/Race	Regimen	Patients	Results
Park 2010	1/2	Korean	**SOX- 3 wk** S-1: 100 mg/m2 Oxaliplatin: 130 mg/m2	n=47 AGC	ORR: 55.3%; TTP: 6.6 m; OS: 12.5 m;
Oh 2012	2	Korean	**SOX- 6 wk** S-1: 80 mg/m2 d1-28 Oxaliplatin: d 1,5,29	n=41 AGC	PR: 53.7%; TTP: 4.6 m; OS: 7.8 m;
Liu 2012	2	Chinese	**SOX-3 wk** S-1: 80 mg/m2 d1-14 Oxaliplatin: 100 mg/m2 d1	n=51 AGC	PR: 41%; TTP: 6.8 m; OS: 11.8 m;
Koizumi 2010	2	Japan	**SOX-3 wk** S-1: 80 mg/m2 d1-14 Oxaliplatin: 100 mg/m2 d1	n=55 AGC	PR: 59%; PFS: 6.5 m; MST: 16.5 m;
Kim 2012	2	Korean	**SOX vs CAPOX-3 wk** S-1: 80 mg/m2 d1-14 Oxaliplatin: 130 mg/m2 d1 Capecitabine: 2000 mg/m2 d1-14	n=129 AGC	ORR: 40% SOX vs 44% CAPOX; TTP: SOX 6.2 m vs CAPOX 7.2 m (p=NS); OS: SOX12.4 m vs CAPOX 13.3 m (p=NS);
Hong 2012	3	Korean	**SOX vs CAPOX-3 wk** S-1: 80 mg/m2 d1-14 Oxaliplatin: 130 mg/m2 d1 Capecitabine: 2000 mg/m2 d1-14	n=340 mCRC	PFS: SOX 8.5 m vs CAPOX 6.7 m; HR: SOX vs CAPOX 0.79 (95%CI 60-1.04);
Higuchi 2013	3	Japan	**SOX vs S-1 cisplatin** SOX: S-1: 80 mg/m2 d1-14 Oxaliplatin 100 mg/m2 d1, 3-wk; S1-cisplatin: S-1: 80mg/m2 d1-21, cisplatin: 60 mg/m2 d8, 5 wk.	n=685 AGC	PFS: SOX 5.5 m vs S-1 cispl 5.4 m; RR: SOX 55.7% vs S1-cispl 52.2% (p=NS)
Chung 2011	1	USA	**SOX-bevacizumab** a)S-1: 25 mg/m2 d1-14	n= NA solid	DLT: diarrhoea

(TPU-S1109)			Oxaliplatin: 130 mg/m2 d1 Bevacizumab 7.5 mg/kg d1 3 wk b)S-1: 35 mg/m2 d1-7 Oxaliplatin: 85 mg/m2 d1 Bevacizumab 5mg/kg d1 2 wk	tumor	

AGC = advanced gastric cancer; CAPOX = capecitabine plus oxaliplatin; mCRC = metastatic colorectal cancer; ORR = overall response rate; OS = overall survival; MST=median survival time; PFS = progression-free survival PR =partial response; SOX = S-1 plus oxaliplatin; TTP = time to progression; NA= Not Available.

Table 3. Efficacy of S1 plus cisplatin.

Study	Phase	Cohort	Dosages	Patients	Endpoints
S1301 FLAGS	3	AGC	S-1 + cisplatin vs 5FU + cisplatin	1053 (EU, USA, Australia, South Africa, Latin America)	**1°: OS** **2°: PFS**
S1101	1/2	AGC	S-1 + cisplatin	88 (USA + Germany)	**1°: MTD (DLT)** **2°: ORR**
91023038 ACTS-GC	3	Adjuvant GC	S-1	1059 (Japan)	**1°: OS**
JCOG 9912	3	AGC	S1 vs 5FU vs cisplatin+irinotecan	704 (Japan)	**1°: OS**
91023039 SPIRITS	3	AGC	S-1 vs S-1+ cisplatin	305 (Japan)	**1°: OS**

2.4.1. Dose response studies

The combination of S1 and cisplatin has been adequately explored in the phase I/II S1101 study conducted in patients with advanced solid tumours and in the phase III S1301 (FLAGS) study conducted in patients with unresectable locally advanced or metastatic gastric cancer. For further information over the combination cisplatin-S1 reference is made to the original EU MAA of S-1.
The combination of S1 with oxaliplatin has been explored in two phase I studies conducted in Caucasians: the TPU-S1119 study exploring the combination S1 + oxaliplatin + epirubicin and the TPU-S1109 trial exploring the combination S1+oxaliplatin + bevacizumab.

2.4.2. Main studies

1) COMBINATION S-1 - OXALIPLATIN

TPU-S1119: A phase 1, open-label, non-randomized, dose-finding, safety and tolerability study of orally administered teysuno (s-1) in combination with epirubicin and oxaliplatin in patients with advanced solid tumours (cohorts 1 and 2) and esophagogastric cancer (cohort 3)

Study participants

The study population was comprised of male and female patients 18 years or older with histologically or pathologically confirmed solid tumour(s) for which no established curative therapy exists (Cohorts 1 and 2) and advanced or metastatic esophagogastric cancer previously not treated (Cohort 3). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 on Cycle 1, Day 1 and a life expectancy of at least 3 months. Patient were able to take medications orally, had left ventricular ejective fraction (LVEF) ≥ the lower limit of normal (LLN) for the institution, had serum troponin T or troponin I and creatine phosphokinase (CPK)-MB values ≤ upper limit of normal (ULN) for the institution, and had adequate organ function.

Study was conducted at 3 sites in Germany and at 3 additional sites in Czech Republic and one site in the United Kingdom.

Treatments

Each treatment cycle was 21 days in duration. One treatment cycle consisted of the following:

Day 1:	- Epirubicin 50 mg/m², via an IV bolus immediately prior to oxaliplatin according to the institution's standard of practice. Epirubicin was limited to a maximum of 8 cycles.
	- Oxaliplatin 130 mg/m², via a 2-hour IV infusion according to the institution's standard of practice. Oxaliplatin was limited to a maximum of 8 cycles.
	- The first S-1 dose (20 mg/m2 or 25 mg/m²) was taken in the evening of Day 1.
Days 2 through 15	- S-1 20 mg/m2 or 25 mg/m² orally 2 times daily on Day 2 through Day 14. The last dose of S-1 per cycle was administered on the morning of Day 15. There was no limit on the number of cycles for S-1.
Days 15 through 21	- Recovery

Cohorts 1 and 2

Patients were assigned to 2 cohorts sequentially. Oxaliplatin 130 mg/m2 and epirubicin 50 mg/m2 doses were fixed and given on day 1 of each 3-week cycle. S-1 dose was escalated by cohort of patients according to the following scheme:

• Dose Level 1: 20 mg/m2 BID (40 mg/m2/day)

• Dose Level 2: 25 mg/m2 BID (50 mg/m2/day)

The first dose of S-1 was administered in the evening of Day 1 of each cycle and twice daily on Days 2 through 14 of each cycle. The last dose of S-1 per cycle was administered on the morning of Day15, followed by a recovery period from Day 15 through Day 21. Oxaliplatin and epirubicin were administered for a maximum of 8 cycles of treatment.

Cohort 3

In Cohort 3 previously untreated patients with advanced esophagogastric cancer were enrolled. Patients received S-1 25 mg/m2 BID (50 mg/m2/day); Oxaliplatin 130 mg/m2 and epirubicin 50 mg/m2 doses were fixed. Patients received S-1 starting the evening of Day 1 of each cycle and BID on Days 2 through 14 of each cycle. The last dose of S-1 per cycle was administered on the morning of Day15, followed by a recovery period from Day 15 through Day 21. Oxaliplatin and epirubicin were administered for a maximum of 8 cycles of treatment.

A dose of 25 mg/m2 of S-1 in the regimen was established as MTD in the second part of the study for esophagogastric patients in first line treatment (Cohort 3).

Objectives

The primary objectives of this study were:

• Pre-Amendment 3 (Cohorts 1 and 2): To investigate the safety and determine the MTD of S-1, either 20 mg/m2 or 25 mg/m2, when combined with epirubicin 50 mg/m2 and oxaliplatin 130 mg/m2 in patients with advanced or metastatic solid tumours.

• Amendment 3 (Cohort 3): To investigate the safety and determine the MTD of S-1 25 mg/m2 when combined with epirubicin 50 mg/m2 and oxaliplatin 130 mg/m2 in patients with advanced or metastatic esophagogastric cancer in the first line therapy.

The MTD was defined as the highest dose level at which less than 33% of the patients experienced a dose-limiting toxicity (DLT) during Cycle 1. After the MTD was determined, up to 6 additional confirmatory patients were to be treated at the MTD level.

Secondary objectives were:

• To document any antitumor activity observed with S-1 administered in this combination treatment regimen

Outcomes/endpoints

- Efficacy Measurements

Tumour assessments were performed and summarized / surveyed to evaluate secondary objectives in the interim report for Cohorts 1 and 2. Antitumor activity observed with S- 1 will be available in the final Clinical Study Report.

The assessment of overall response rate (ORR) was based on Investigator-supplied objective measures of disease after review of radiologic images, computed tomography (CT) or magnetic resonance imaging (MRI) scans, and following RECIST criteria (version 1.1 2009). Overall response rate was defined as the proportion of patients with objective evidence of CR or PR. Patients were assigned to one of the categories of change in disease state, namely, “complete response (CR),” “partial response (PR),” “stable disease (SD),” “progressive disease (PD),” or “not evaluable (NE).” Efficacy data were based on tumour response using RECIST criteria assessed every 3 cycles.

Progression free survival (PFS) was defined as the time (in months) from the date of first dose of S-1 until the date of the investigator-assessed radiological disease progression, clinical 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. An additional analysis was based on only radiologic images (i.e. excluding clinical progression). Patients with clinical but not radiologic evidence of progression were censored at the date of the last radiologic tumour assessment.

Overall survival (OS) was defined as time from the first dose of S-1 to the date of death. Patients who did not die were censored at the date last known to be alive.

Treatment was to be continued until disease progression, intolerable toxicity, or withdrawal of consent. Each patient was followed for survival every 2 months for up to 12 months after the first dose of study medication.

- Safety Measurements

Safety assessments included determination of the incidence, severity, and causality of AEs and SAEs and other safety parameters as follows:

• Physical examination

• Vital signs

• ECOG performance status

• 12-lead ECG

• ECHO

• Cardiac Enzymes

• Clinical laboratory evaluations

• Pregnancy monitoring

Sample size

Each dose level in study TPU-S1119 involved a minimum of 3 patients. Escalation to Dose Level 2 (Cohort 1 only) occurred only after Dose Level 1 was found to be safe according to the protocol criteria.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

The study populations included safety, DLT evaluable, and efficacy populations.

Safety Population

The safety population included all patients who received at least one dose of study medication. This population was the primary population for safety evaluation.

DLT Evaluable Population

The DLT evaluable population included all patients in the safety population who completed at least one cycle of study medication with at least 80% treatment compliance, unless treatment was interrupted due to a DLT.

Efficacy Population

The efficacy evaluable population included all patients in the safety population who completed at least one cycle of study medication and had radiologic or clinical progression assessments performed. In this interim report, efficacy data were presented for Cohorts 1 and 2.

RESULTS

Patient Disposition:

Nineteen (19) patients were enrolled in the study, 3 patients in Cohort 1, 6 patients (5 DLT evaluable) in Cohort 2, 3 patients in expanded Cohort 1, and 7 patients in Cohort 3.

As of the cut-off date (30 April 2014) for the interim report, 7 patients in Cohort 3 were treated and the study was completed for 3 out of the 7 patients. All patients in Cohorts 1 and 2 had completed the study. Twelve (63.2%) patients were male and 7 (36.8%) were female with a median age of 63 years (range, 48 to 77 years). All patients were Caucasian. Ten (52.6%) patients had an ECOG performance status score of 0 and 9 (47.4%) patients had an ECOG score of 1 at baseline. Fourteen (73.7%) patients had previous surgery and 5 (26.3%) patients had no previous surgery. In Cohorts 1 and 2, 7 (36.8%) patients had previous systemic anticancer therapies: 5 (26.3%) patients had one, 2 (10.5%) had two previous therapies, which included one or more of the following: capecitabine, carboplatin, cisplatin, erlotinib, and/or gemcitabine. In Cohort 3 (chemotherapy-naïve patients), no patients had a previous systemic anticancer therapy.

Table 4. Patient disposition TPU-S1119 study

	20 mg/m^2 Cohort 1	25 mg/m^2 Cohort 2	25 mg/m2 Cohort 3a	All Patients
Populations:				
Enrolled but not Treated				11
Safety (No. Patients Dosed)	6 (100.0)	6 (100.0)	7 (100.0)	19 (100.0)
Reason for Discontinuation from Study Treatment[b]:				
Discontinued	6 (100.0)	6 (100.0)	3 (42.9)	15 (78.9)
Adverse Event/SAE	2 (33.3)	1 (16.7)	1 (14.3)	4 (21.1)
Clinical Disease Progression	0	0	1 (14.3)	1 (5.3)
Radiologic Progression	4 (66.7)	3 (50.0)	0	7 (36.8)
Patient Withdrew Consent for Study Treatment	0	0	0	0
Other	0	2 (33.3)	1 (14.3)	3 (15.8)
Reason for Discontinuation from Study				
Patient Died	5 (83.3)	3 (50.0)	0	8 (42.1)

	20 mg/m^2 Cohort 1	25 mg/m^2 Cohort 2	25 mg/m2 Cohort 3a	All Patients
Study is Completed or Terminated	0	1 (16.7)	0	1 (5.3)
Ongoing/Completed Study as of 30Apr2014[c]	0	0	7 (100.0)	7 (36.8)

[a] Advanced Esophagogastric Cancer - Amendment 3.
[b] Reasons for Discontinuation from Study Treatment provided for only those patients enrolled and treated.
[c] For Cohorts 1 and 2, all subjects have been discontinued from study follow-up or have completed 12 months follow-up.

Data are based on the cut-off date of 30 April 2014.

MTDs

Cohort 1 and 2: The dose of S-1 20 mg/m2 BID was established as the MTD of S-1 in the EOS triplet. DLTs occurred in patients with non-esophagogastric tumours in the third line treatment.

Cohort 3: A dose of 25 mg/m2 of S-1 in the regimen was established as MTD in the second part of the study for esophagogastric patients in first line treatment.

Efficacy evaluation

Efficacy evaluations (i.e., best overall response, OS, and PFS) were performed for 12 patients in Cohorts 1 and 2 at the interim report. The efficacy evaluation of the results of the TPU-S1119 study is seriously hampered by the very low number of patients treated. Moreover, results are related to the

Cohort 1 and 2 of the study, where patients with solid tumours in general and not only patients as indicated in the target population, were enrolled.

Best Overall Response

Three out of six (3/6, 50%) patients who received S-1 the 20 mg/m2 BID dose (cohort 1) were evaluable for response. Stable disease was reported in 1 patient (1/6, 33.3%) and progressive disease in 2 patients (2/3, 66.7%). Three out of six patients (3/6, 50%) who received the 25 mg/m2 BID S-1 dose were evaluable for response (cohort 2). Two patients in cohort 2 had stable disease (2/3, 66.7%) and 1 had progressive disease (1/3, 33.3%).

Table 5. Best Overall Response – Cohorts 1 and 2

Parameter	20 mg/m^2 Cohort 1 (N=6)	25 mg/m^2 Cohort 2 (N=6)
Best Overall Response, n (%)		
Complete or Partial	0	0
Stable Disease (SD)	1 (16.7)	2 (33.3)
Progressive Disease – Radiological (PD)	2 (33.3)	1 (16.7)
Not Evaluable	3 (50.0)	3 (50.0)
Not Assessed	0	2 (33.3)
Censored – Due to Other Anti-Tumor Rx	3 (50.0)	1 (16.7)

Preliminary data of Cohort 3 (treated with 25 mg/m2 BID S-1 dose) reported one patient progressed after a best overall response of stable disease.

Progression free Survival

The median PFS was 1.9 months for patients in Cohort 1 and 3.9 months (95% CI: 1.9, 1.9) for patients in the Cohort 2 (95% CI: 2.0, 11.2).

Overall Survival

At least 15 months follow-up data were available for all patients in Cohort 1 and 2. Median OS was 5.8 months for Cohort 1 (95% CI: 4.5, 13.1) and 8.7 months for Cohort 2 (95% CI: 6.5, -). The 1-year Kaplan-Meier survival estimate was 33.0% in Cohort 1 and 44.4% in Cohort 2.

TPU-S1109 trial

TPU-S1109 was a phase 1 dose escalation study in patients with advanced solid tumours designed to identify the MTD of S-1 when used in combination with fixed doses of oxaliplatin and bevacizumab in 2- or 3-week treatment regimens and to determine whether there were any PK interactions between S-1 components and oxaliplatin. No clinical study report related to this study, but only a literature reference, has been provided. This hampers adequate assessment of the data provided. The limited number of patients treated and the lack of information related to the number of patients with advanced gastric cancer eventually enrolled in this study further challenge the interpretation of the results. Furthermore, currently bevacizumab is not registered for the treatment of advanced gastric cancer.

Stage A was a 3-week cycle in which S-1 was started at 20 mg/m2 twice daily for 14 consecutive days, and escalated by 5 mg/m2, plus oxaliplatin (130 mg/m2 IV) and bevacizumab (7.5 mg/kg IV) on day 1 of each 3-week cycle.

Stage B was a 2-week cycle of S-1 administered at 25 mg/m2 twice daily for 7 consecutive days, and escalated by 5 mg/m2, plus oxaliplatin (85 mg/m2 IV) and bevacizumab (5 mg/kg IV) on day 1 of each 2-week cycle.

Efficacy data were analysed using Response Evaluation Criteria in Solid Tumours (RECIST Criteria version 1.1). CT-scans were performed every 2 cycles.

Antitumor activity was evaluated in terms of objective response rate (ORR) and progression-free survival (PFS). Overall survival (OS) at 12 months was also summarized.

For Stage A, 23/24 (95.8%) patients were included in the Efficacy Population. One patient (patient 001-024, 25 mg/m2 dose group) was not evaluable for efficacy due to the lack of post-baseline tumour assessment. Two (2/23, 8.7%) patients in the 25 mg/m2 dose group had a partial response to S-1 combination treatment, 17 (73.9%) patients had a best overall response of stable disease and 4 (17.4%) patients had progressive disease.

For Stage B, 23/24 (95.8%) patients were included in the Efficacy Population. Patient 001-041 (35 mg/m2 dose group) was not evaluable for efficacy due to the lack of a post-baseline tumour assessment. Eight (34.8%) patients across all dose groups had a partial response to S-1 combination treatment, 10 (43.5%) patients had a best overall response of stable disease, and 5 (21.7%) patients had progressive disease.

2) COMBINATION S-1 - CISPLATIN

The efficacy of the combination S-1 –cisplatin has been established during the original EU MAA for S-1. Evidence of the anti-tumour activity of S-1 in combination with cisplatin for the treatment of patients with gastric cancer was provided by three Phase 3 studies conducted in advanced gastric cancer (JCOG 9912, 91023039/SPIRITS and S1301/FLAGS), all of which had a primary endpoint of overall survival. Study S1301/FLAGS is considered the pivotal source of efficacy of S-1 in combination with cisplatin in Western population. Supportive efficacy data was provided by one Phase 1/2 study conducted in the US and Germany (S1101).

The pivotal S1301/FLAGS [First-Line Advanced Gastric Study] study was an open-label randomized Phase III clinical trial that evaluated S-1 + Cisplatin versus 5-FU + Cisplatin in patients with advanced gastric cancer previously untreated with chemotherapy for advanced disease. Results from the study revealed non-inferiority of the S1+Cisplatin combination compared with 5FU+cisplatin in terms of overall survival (median OS 8.6 vs 7.9 months with S1+cisplatin and 5FU+cisplatin, respectively, HR 0.92, 95% CI: 0.80-1.05, p=0.1983) and other clinically relevant secondary endpoints like PFS, ORR, duration of response, time to progression.

Further information is available in the EPAR related to the original MAA for Teysuno.

3) COMBINATION S-1 - CARBOPLATIN

No data have been provided by the MAH regarding the efficacy of the combination S1+carboplatin in patients with advanced gastric cancer nor in Caucasians.

Few abstracts/articles are available in the literature regarding phase I-III studies with the combination S1+carboplatin in Japanese patients with NSCLC (Tamura K et al JCO 2006, Yoshioka H et al Ann Oncol 2013, Urata Y et al Cancer 2013).

Summary of main study(ies)

N/A.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

The small number of patients treated with the combination S-1+ epirubicin + oxaliplatin hampers efficacy evaluation in different populations and ages categories.

2.4.3. Discussion and Conclusions on the Clinical Efficacy

The present type II variation appears to be supported by the results of studies where oxaliplatin substituted cisplatin. However the proposed wording of indication is more general as “platinum-based regimens” would include also “carboplatin-based regimens”. No data regarding the combination Carboplatin-S1 have been provided.

The efficacy of S1 in combination with cisplatin has been explored in the pivotal phase III (FLAGS) study, comparing the combination S1+ cisplatin with 5FU+cisplatin in the target population. The non-inferiority of the combination S1+ cisplatin versus S1+ 5FU has been assessed during the original submission regarding the MAA of Teysuno in patients with advanced gastric cancer and is considered demonstrated.

Essentially, the modification of the wording of the indication in order to substitute the compound “cisplatin” with the generic diction “platinum-based regimen” is based on the interim analysis of one phase I dose-finding study (TPU-S1119) conducted with S1+ oxaliplatin + epirubicine, in Caucasian patients with advanced solid tumors (Cohort 1 and 2) and in 7 patients with advanced esophagogastric cancer (cohort 3) where apparently no PK data in order to exclude an interaction were collected.

The design and the number of patients treated in the study do not allow a compelling evaluation of the efficacy of the scheme in the target population as proposed.

Other studies reported in the literature are mentioned, but, with the exception of another phase I study (TPU-S1109) published by Chung et al., which was conducted in USA, all the other articles are related to study performed in Asians. In the phase I TPU-S1109 study, PK data over the combination oxaliplatin + S1 + bevacizumab were collected, but no clinical study report has been provided by the MAH. Extrapolation of efficacy and safety from Asians to Caucasians is not readily acceptable due to potential racial differences in efficacy and safety of S-1 (for instance, racial differences in CYP2A6 and related SNPs lead to difference in tegafur metabolism), as well as in the biology and natural history of gastric cancer. Moreover, evaluation of the supportive studies is hampered by the lack of compelling information regarding such studies, as only published articles have been reported. Furthermore, it should be noted that in all the studies reported in the literature with S1 in combination with oxaliplatin and performed in non-Caucasian patients, the dose and scheme of S1 used are different from the one proposed for registration in EU

No efficacy data have been provided over S-1 in combination with carboplatin (another clinically used platinum compound).

Data are considered too scarce to allow adequate evaluation of the efficacy of S1 in combination with platinum compounds –other than cisplatin in the target population of advanced gastric cancer.

Extrapolation of the known efficacy results of 5FU/capecitabine in combination with platinum regimens in the target population to S-1 is not considered appropriate, in view of the known differences in pharmacological characteristics, mechanism of action, schema/dosing regimen and toxicity between the platinum compounds available.

2.5. Clinical safety

2.5.1. Introduction

The safety database that establishes the foundation for this type II variation of S-1 (Teysuno, TS1) in combination with **platinum-regimens** in patients with advanced gastric cancer is based on:

1- Regarding the combination Oxaliplatin-S1:

   a. the interim results of the phase 1, open-label dose-finding TPU-S1119 study where S-1 was administered in combination with oxaliplatin and epirubicin in patients with advanced solid tumours (Cohort 1 and 2) and in 7 patients with esophagogastric cancer (cohort 3);

   b. the phase I TPU-S1109 trial, where patients with advanced solid tumours were treated in USA with the combination S1-oxaliplatin-bevacizumab, in a 3-weekly (Stage A) and in a 2-weekly (Stage B) schema;

2- Regarding the combination Cisplatin-S1:

   a. The database provided/assessed during the original MAA in EU of S-1 in combination with cisplatin in patients with advanced gastric cancer. These data will be discussed in summary as they have been already assessed previously. For more information reference is made to the original EU MAA of Teysuno.

The safety database in support of this type II variation consists of around 600 patients with advanced gastric cancer treated with Teysuno in combination with a platinum based regimen, the great majority of which (98%) treated with S1+ cisplatin.

TPU-S1119 trial

Patient exposure

Patients were assigned to 2 cohorts sequentially. Oxaliplatin (130 mg/m2) and epirubicin (50 mg/m2) doses were fixed. S-1 dose was escalated by cohort of patients according to the following scheme:

- Cohort 1: 20 mg/m2 BID (40 mg/m2/day) – advanced solid tumours (part 1)
- Cohort 2: 25 mg/m2 BID (50 mg/m2/day) – advanced solid tumours (part 1)
- Cohort 3: 25 mg/m2 BID (50 mg/m2/day) – oesophagogastric cancer (AEGC, part 2)

Escalation to Dose Level 2 (cohort 2) occurred only after Dose Level 1 was found to be safe according to the protocol criteria. Intra-patient dose escalation was not allowed. The MTD was defined as the highest dose level at which less than 33% (≤1/6) of the patients experienced a dose-limiting toxicity (DLT) during Cycle 1. Once the MTD was established, the cohort was to be expanded to up to 12

patients. The DLT evaluable population included all patients in the safety population who completed at least one cycle of study medication with at least 80% treatment compliance, unless treatment was interrupted due to a DLT. A DLT was defined as the following:

a. ≥ Grade 3 non-hematologic toxicity (excluding nausea/vomiting, diarrhoea).

b. ≥ Grade 3 nausea/vomiting uncontrolled by aggressive antiemetic support.

c. ≥ Grade 3 diarrhoea lasting more than 24 hours despite antidiarrheal treatment.

d. Febrile neutropenia (absolute neutrophil count [ANC] <1.0 x 109/L with a single temperature of >38.3°C or a sustained temperature of >38°C for more than one hour).

e. Grade 4 neutropenia lasting ≥5 days.

f. Grade 4 thrombocytopenia associated with dose interruption or hemorrhage.

g. Any drug-related toxicity resulting in >1 week delay in initiation of Cycle 2 (i.e., cannot start Cycle 2 until Day 29 or later).

h. Any drug-related toxicity that results in administration of <80% of total planned S-1 dose.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities was graded according to the NCI CTCAE, v4.03.

Twelve (11 DLT evaluable) patients with solid tumours with any number of previous therapies for advanced or metastatic disease were enrolled. No DLTs were observed in Cohort 1 (S-1 20 mg/m2 BID). Two patients in Cohort 2 reported DLTs (Grade 3 elevated gamma GT and peripheral neuropathy in one patient, and febrile neutropenia in another patient who died five days later due to pneumonia).

The MTD in an AEGC population who receive EOS as first-line treatment might be potentially higher, therefore, a new cohort of previously untreated AEGC patients (Cohort 3) was administered 25 mg/m2 S1 BID in combination with oxaliplatin 130 mg/m2 and epirubicin 50 mg/m2 (Amendment 3) to determine the MTD in this population. Six of 7 patients enrolled in Cohort 3 were evaluable for DLT assessment, no DLTs occurred in Cycle 1. The dose of S-1 25 mg/m2/dose BID was established as the MTD of S-1 in the EOS triplet for chemo-naïve patients with esophagogastric tumours.

A total of 8 (42.1%) patients had at least 4 cycles of treatment. Three (15.8%) patients had >4 cycles initiated. One patient (5.3%) initiated a maximum of 15 cycles. A mean of 3.7 cycles and median of 3.0 cycles were initiated by all patients.

Adverse events

The safety reported for the combination is related to an interim preliminary safety evaluation including 19 patients who had completed Cycle 1 of the study as of the cut-off date of 30 April 2014, including 6 patients in Cohort 1 (20 mg/m2 BID), 6 patients in Cohort 2 (25 mg/m2 BID) and 7 patients in Cohort 3 (25 mg/m2 BID).Number are considered too small to allow adequate evaluation of the safety of the combination in the target population.

No DLTs were observed in Cohort 1 (S-1 20 mg/m2 BID). Two patients in Cohort 2 reported DLTs: one patient experienced DLTs of Grade 3 elevated gamma GT and peripheral neuropathy, and another patient (with generalized cholangiocarcinoma and two courses of previous chemotherapy) experienced DLT of febrile neutropenia on the Day 9 of Cycle 1 and died five days later due to pneumonia. A patient in cohort 3 experienced grade 3 AST increase and grade 4 neutropenia on day 12 of Cycle 1 but was not DLT evaluable as eligibility criteria were violated due to alcohol abuse.

As of the cut-off date of 10 April 2014 (all patients; Cohorts 1, 2, and 3), the most frequently reported treatment-emergent AEs were anaemia (n=5 patients), neutropenia (n=10), thrombocytopenia (n=6), abdominal pain (n=4), diarrhoea (n=8), nausea (n=11), vomiting (n=8), fatigue (n=8), neuropathy peripheral (n=4), paraesthesia (n=8), and alopecia (n=5). The most frequently reported study medication related AEs were neutropenia (n=9 patients), thrombocytopenia (n=6), diarrhoea (n=6), nausea (n=8), vomiting (n=4), fatigue (n=4), and alopecia (n=5).

Grade 4 reported AEs include neutropenia (n=2 patients, n=1 in Cohorts 1 and 3), febrile neutropenia (n=1, Cohort 2), hyponatraemia (n=1, Cohort 2), and renal failure acute (n=1; Cohort 1). Grade 3 reported AEs include neutropenia (n=7), thrombocytopenia (n=3), nausea (n=1), fatigue (n=1), general physical health deterioration (n=1), bile duct stenosis (n=2), hypersensitivity (n=1), gamma-glutamyltransferase increased (n=1), neutrophil count decreased (n=1), neuropathy peripheral (n=1), and hypotension (n=1).

Grade 5 study medication-related AEs included pneumonia (n=1, Cohort 2). Grade 4 study medication related AEs included neutropenia (n=2 patients, Cohorts 1 and 3) and febrile neutropenia (n=1, Cohort 2). Grade 3 study medication related AEs included neutropenia (n=6), thrombocytopenia (n=3), nausea (n=1), fatigue (n=1), gammaglutamyltransferase increased (n=1), and neutrophil count decreased (n=1).

Patients enrolled in the TPU-S1119 study were required to have adequate left ventricular ejection fraction at baseline. According to the study protocol, Echocardiogram, ECG and evaluation of cardiac enzymes were regularly performed in patients enrolled in the study. The MAH should clarify whether reductions of left ventricular ejection fraction or other cardiac adverse events/significant abnormalities were observed in the patients treated and whether such findings should result to inclusion of a warning over this issue in the SmPC.

Serious adverse event/deaths/other significant events

Nineteen (19) treatment-emergent SAEs occurred in 9 patients. The majority of SAEs resolved except acute renal failure in patient 001-010, hyperbilirubinemia and bile duct stenosis in patient 001-011, general physical health deterioration in patient 005-101, and patient 001-005 - the patient died. Six of these SAEs that occurred in 2 patients were S-1 related: neutropenia in patient 001-001; and pneumonia, cholangitis, thrombocytopenia, sepsis, and febrile neutropenia in patient 001-005.

Safety in special populations

No specific data have been provided. The small number of patients treated with the combination S-1+ epirubicin + oxaliplatin hampers the evaluation of the toxicity in different populations and age categories.

Discontinuation due to adverse events

Cohort 1 – 20 mg/m2

• Patient 1 completed 4 cycles with S-1 dose reduction to 15 mg/m2 in Cycle 3 and 4 due to Grade 3 thrombocytopenia. The treatment had been stopped due to the disease progression.

• Patient 2 completed 3 cycles without S-1 dose reduction. The treatment had been stopped due to the disease progression.

• Patient 3 completed 4 cycles with S-1 dose reduction to 15 mg/m2 in Cycle 2. The treatment was interrupted on Day 8 of Cycle 3 due to Grade 3 thrombocytopenia.

• Patient 4 completed 4 cycles with S-1 dose reduction to 15 mg/m2 in Cycle 2 due to a decrease in BSA from 1.93 m2 (80 mg dose) to 1.8 m2 (70 mg dose). In Cycle 4, S-1 was discontinued due to acute renal failure.

• Patient 5 completed 4 cycles with S-1 dose reduction to 15 mg/m2 in Cycle 2 due to a decrease in BSA from 2.2 m2 (90 mg dose) to 2.1 m2 (80 mg dose). The treatment was stopped in Cycle 4 due to Grade 3 hyperbilirubinemia and disease progression.

• Patient 6 completed 3 cycles without S-1 dose reduction. The treatment had been stopped due to the disease progression.

Cohort 2 – 25 mg/m2

• Patient 7 completed 10 cycles with S-1 dose reduction to 20 mg/m2 in Cycle 6. The treatment was stopped due to the disease progression.

• Patient 8 had S-1 treatment discontinued on Day 9 of Cycle 1 due to a DLT (Grade 4 febrile neutropenia). The patient died 5 days later due to pneumonia.

• Patient 9 completed 3 cycles with S-1 dose reduction to 15 mg/m2 in Cycle 3. The treatment was interrupted in Cycle 1 due to the planned anaesthesia for stent implantation. Due to a low S-1 compliance (71%) the patient was not evaluable (the limit was ≥ 80%).

• Patient 10 completed 15 cycles with S-1 dose reduction to 20 mg/m2 in Cycle 2. The treatment was stopped due to disease progression.

• Patient 11 had S-1 treatment discontinued on Day 8 of Cycle 1 due to a DLT (elevation of Gamma GT-Grade 3 non-hematologic toxicity).

• Patient 12 completed 6 cycles with S-1 dose reduction to 20 mg/m2 from Cycle 4. The treatment was stopped due to the disease progression.

The S-1 dose in patients 7, 10 and 12 was reduced after the second DLT occurred in the Cohort 2. It was decided that at all ongoing patients in the cohort 2 (25mg/m2), the dose should be reduced to 20mg/m2 at the beginning of their next cycle.

Cohort 3 – 25 mg/m2 (preliminary data – cut-off date April 30, 2014)

• Patient 13 completed Cycle 1 without DLT. The treatment was ongoing as of the cut-off date.

• Patient 14 completed Cycle 1 without DLT. The treatment was ongoing as of the cut-off date.

• Patient 15 completed Cycle 1 without DLT. The treatment was ongoing as of the cut-off date.

• Patient 16 completed 4 cycles without S-1 dose reduction. The treatment was discontinued after Cycle 4 due to disease progression.

• Patient 17 had S-1 treatment interrupted on Day 12 of Cycle 1 due to Grade 3 AST increase and other AEs. This patient had not met eligibility criteria, therefore was not DLT evaluable.

• Patient 18 completed Cycle 1 without DLT.

• Patient 19 completed Cycle 1 without DLT. The treatment was discontinued after Cycle 1 due to dysphagia related to the oesophageal stent replacement.

TPU-S1109 Trial

Only a literature reference has been provided regarding the supportive dose-escalating trial TPU-S1109 conducted in USA with the combination S1-Oxaliplatin-bevacizumab in patients with advanced solid tumours (Chung KY, 2011). Two schedules were evaluated:

-Schedule A: S-1 was administered orally (at a starting dose of 20 mg/m2 and cohort dose escalation by 5 mg/m 2 increments), twice daily for 14 consecutive days followed by a 7-day recovery period in a 21-day cycle. Oxaliplatin 130 mg/m2 and bevacizumab 7.5 mg/kg were administered intravenously in fixed doses on day 1 of each 3-week cycle. Oxaliplatin was stopped after 4 cycles of treatment. A minimum

-Schedule B: S-1 was administered orally (at a starting dose of 25 mg/m2, with cohort dose escalation by 5 mg/m2 increments), twice daily on day 1 for 7 consecutive days followed by a 7-day recovery period in a 14- day cycle. Oxaliplatin 85 mg/m2 and bevacizumab 5 mg/kg were administered intravenously in fixed doses on day 1 of each 2-week cycle. Oxaliplatin was stopped after 6 cycles of treatment.

According to the article published adverse events (AEs) were collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. A DLT that occurred during the first 2 cycles for schedule A and the first 3 cycles for schedule B was defined as: grade > 3 non-hematologic toxicity including nausea, vomiting and diarrhoea uncontrolled by aggressive treatment, febrile neutropenia, grade 4 neutropenia or thrombocytopenia, or any failure of the patient to take > 80% of the planned S-1 treatment. The S-1 as well as oxaliplatin doses were reduced or delayed if patients experienced unacceptable drug-related toxicity. The MTD was defined as the highest dose level at which < 33% of patients experienced a DLT during the first 2 cycles for schedule A and the first 3 cycles for schedule B. Once the MTD was determined, additional 6–12 patients were to be treated at the same level.

In the schedule A with 30-mg/m2 S1 dose, 2 out of 6 patients treated experienced DLTs: 1 patient with metastatic pancreatic adenocarcinoma experienced grade 3 diarrhoea on day 15 of cycle 2 despite aggressive antidiarrheal treatment, and 1 patient with recurrent metastatic undifferentiated nasopharyngeal carcinoma developed grade 3 mucositis after the first cycle, tolerating the subsequent dose level of S-1 (25 mg/m2) without toxicity.

In the Schedule B with 40-mg/m2 S1 dose, 2 out 6 patients treated developed DLTs (1 patient with grade 3 diarrhoea, fatigue, dehydration, proteinuria, nausea and vomiting, and 1 patient with grade 4 neutropenia, grade 3 diarrhoea, rectal bleeding and dehydration). Two out of additional 9 patients treated in the 35-mg/m2 expansion cohort developed DLTs: one patient experienced grade 3 abdominal pain and another patient experienced grade 3 diarrhoea.

Adverse events

-Schedule A. According to the published article, only grade 3 fatigue was reported in the 20-mg/m2 dose group. In the 25-mg/m2 dose group, grade 3 (nausea, vomiting, fatigue, diarrhoea, dehydration, abdominal pain, hyperbilirubinemia, proteinuria) and a grade 3 hypersensitivity reaction to oxaliplatin were each reported in 1 patient (7%). In the 30-mg/m2 dose group, grade 3 neutropenia, thrombocytopenia, nausea, dehydration and proteinuria were each reported in 1 patient (7%) and diarrhoea in 2 patients (29%). In the 25-mg/m 2 MTD dose group, the most common treatment-related AEs were fatigue (71%), nausea (64%), diarrhoea (50%), anorexia (50%) and peripheral sensory neuropathy (43%). Hematologic AEs included thrombocytopenia (43%) with no grade 6 3 bone marrow suppression reported.

-Schedule B. All patients experienced at least 1 treatment-related AE. No grade 3 or 4 treatment-related AEs were reported in the 25-mg/m2 dose group. In the 30-mg/m2 dose group, grade 3 leukopenia, thrombocytopenia and hyperbilirubinemia were each reported in 1 patient (33.3%). In the 35-mg/m2 MTD dose group, grade 3 anaemia, thrombocytopenia, abdominal pain and hyperbilirubinemia were each reported in 1 patient (8.3%), and grade 3 fatigue and diarrhoea were each reported in 2 patients (17%). In the 35-mg/m2 MTD dose group, the most common AEs were fatigue (75%), diarrhoea (58%) and anorexia (58%).

S-1 in combination with Cisplatin

The marketing authorisation of S-1 in combination with Cisplatin (for the indication of first line treatment of advanced gastric cancer) was mainly based on the results of the S1301/FLAGS study, an open-label phase III trial performed in a predominantly Caucasian population that randomly compared treatment with S1+ Cisplatin versus infusional 5FU + Cisplatin in patients with advanced gastric cancer. S-1 was given at the dose regimen established in US and European patients (i.e., 25 mg/m2 S-1 twice daily for 21 consecutive days) with 75 mg/m2 cisplatin administered in Day 1, and repeated every 28 days.

The S-1 + cisplatin regimen demonstrated a superior safety profile compared to that of the 5-FU + cisplatin regimen in the S1301/FLAGS study, with clinically important differences in haematologic and non-haematologic toxicity, as well as a lower incidence of toxic deaths compared to the 5-FU + cisplatin regimen. The lower incidence of GI toxicity, particularly stomatitis and mucosal inflammation, appeared to be related to S-1 administration, whereas the reduction of haematologic and renal toxicity was probably related to both S-1 and the lower dose of cisplatin used in the S-1 + cisplatin arm.

The overall incidence of Grade > 3 adverse events was lower in the S-1 + cisplatin group than in the 5-FU + cisplatin group in terms of neutropenia, leukopenia, febrile neutropenia, stomatitis, and mucosal inflammation. Grade 3-4 neutropenia (that worsened from baseline by at least one grade) was observed half as frequently in the S-1 + cisplatin group (32.3% of patients) as in the 5-FU + cisplatin group (63.6%), and events of febrile neutropenia or neutropenic infection were significantly lower in the S-1 + cisplatin arm (5.0%) than in the 5-FU + cisplatin arm (14.4%). Deaths due to drug-related events indicative of myelosuppression were observed in 4 (0.8%) patients in the S-1 + cisplatin arm compared to 14 (2.8%) patients in the 5-FU + cisplatin arm. Overall, the frequency of toxic deaths in the S-1 + cisplatin arm (2.5% of patients) was approximately half that of the 5-FU + cisplatin arm (4.9% of patients). In addition, the overall incidence of Grade 3-4 stomatitis/mucosal inflammation was significantly lower in the S-1 + cisplatin group compared to the 5-FU + cisplatin group (2.1% versus 21.5%). There was no difference between the S-1 + cisplatin and 5-FU + cisplatin treatment groups with respect to incidence of Grade 3-4 diarrhea (4.8%, S-1 + cisplatin; 4.5%, 5-FU + cisplatin). As expected due to the lower dose of cisplatin in the S-1 + cisplatin arm, significantly fewer abnormalities in renal-related laboratory parameters, such as elevated serum creatinine and impairment of renal clearance, but also peripheral neuropathy, and alopecia were observed in the S-1 + cisplatin arm compared to the 5-FU + cisplatin arm.

Events of palmar-plantar erythrodysaesthesia were reported more frequently in the S-1 + cisplatin arm than in the 5-FU + cisplatin arm (5.4% versus 2.6%), but were limited to Grade 1 or 2 severity in almost all patients. Clinical laboratory findings of Grade 3-4 hyperbilirubinaemia were more frequent in the S-1 + cisplatin arm than in the 5-FU + cisplatin arm (6.5% vs 3.6%), but were not associated with parenchymal hepatotoxicity.

Post marketing experience

The safety profile of Teysuno in a post-marketing safety surveillance study in Japan of 4177 patients treated with Teysuno, as monotherapy or in combination regimens, for advanced gastric cancer was generally in line with the expected toxicity profile, with most frequently reported adverse events being leucocytopenia, anorexia, and nausea/vomiting.

2.5.2. Discussion and Conclusions on clinical safety

The safety database that establishes the foundation for this type II variation of S-1 (Teysuno, TS1) in combination with platinum-regimens in patients with advanced gastric cancer is based on around 600 patients, the great majority of which (>98%) treated with the combination S1+ cisplatin. They include:

- the interim safety results of the phase 1, open-label dose-finding TPU-S1119 study where S-1 was administered in combination with oxaliplatin and epirubicin in patients with advanced solid tumours (Cohort 1 and 2) and in 7 patients with esophagogastric cancer (cohort 3);

- the article reported in the literature (Chung 2011) regarding the phase I TPU-S1109 trial, where patients with advanced solid tumours were treated in USA with the combination S1-oxaliplatin-bevacizumab, in a 3-weekly (Stage A) and in a 2-weekly (Stage B) schema;

- the database provided/assessed during the original MAA in EU of S-1 in combination with cisplatin in patients with advanced gastric cancer.

Of note, no data have been provided regarding the combination of S-1 with carboplatin, another clinically used platinum-compound.

The data regarding the toxicity of the combination S-1 + cisplatin are in line with the already known safety database. The very limited data available over the combination Oxaliplatin-epirubicin-S1 and S-1-Oxaliplatin-bevacizumab appear to suggest a safety profile of the combinations explored in line with the drug class and mechanism of action and with baseline characteristics of the study population (patients with solid tumours and advanced esophagogastric cancer), but evaluation could be confounded by the drug specificic toxicity of epirubicin or bevacizumab and by the small safety database. Although no pharmacokinetic interactions appear to be observed with the combination S-1 and Oxaliplatin in the studies presented, the paucity of data due to the very limited number of patients treated, the heterogeneity of S-1 dose administered and the short follow up do not allow a compelling evaluation of the safety profile of S-1 in combination with platinum compounds, other than cisplatin.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

Please refer to PRAC Rapporteur's RMP AR.

2.7. Update of the product information

As a consequence of this type II variation, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC have been updated. Particularly, the wording of indication has been modified in order to substitute the text "Teysuno is indicated in adults for the treatment of advanced gastric cancer when

given in combination with cisplatin" with "Teysuno is indicated in adults for the treatment of advanced gastric cancer when given in **combination with a platinum-based regimen**". The results of the phase I studies TPU-S1119 and TPU-S1109 have been added to section 5.1 of the SmPC. The Package Leaflet has been updated accordingly.

Proposed changes to the SmPC are included as an appendix to this report.

3. Benefit-risk balance

Benefits

Beneficial effects

The efficacy of S1 in combination with cisplatin has been adequately demonstrated in the pivotal phase III (FLAGS) study, comparing the combination S1 + cisplatin with 5FU + cisplatin in the target population. The non-inferiority of the combination S1 + cisplatin versus 5FU + cisplatin has been assessed during the original submission of the MAA of Teysuno in patients with advanced gastric cancer leading to a positive CHMP opinion.

Uncertainty in the knowledge about the beneficial effects

Pharmacokinetics data regarding potential interaction between S1 + oxaliplatin + epirubicin have not been provided.

No Clinical Study Report has been provided for study TPU-S1109 which was intended to support the use of S1 in combination with oxaliplatin from a PK viewpoint. This hampers an adequate assessment of the claimed lack of pharmacokinetic interaction between S1 and oxaliplatin.

The efficacy data in support of the combination S1-Oxaliplatin are based one phase I dose-finding TPU-S1119 study (where the combination S1 + oxaliplatin + epirubicin was evaluated in patients with advanced solid tumors (Cohort 1 and 2) and in 7 patients with advanced esophagogastric cancer previously untreated (cohort 3). Supportive literature data from the dose-finding TPU-S1109 study exploring the combination S1 + oxaliplatin + bevacizumab conducted in patients with advanced solid tumors have been provided. Data are too scarce to adequately evaluate the efficacy of the S1-oxaliplatin combinations in the proposed target population.

No efficacy data have been provided over S1 in combination with carboplatin (another clinically used platinum compound).

In view of the known differences in pharmacological characteristics, mechanism of action, dosing regimen and toxicity between the platinum compounds available, extrapolation of the data available over efficacy and safety of S1-Cisplatin to other platinum-based combinations is not considered appropriate.

Risks

Unfavourable effects

The safety of S1 in combination with cisplatin has been adequately assessed, in comparison with 5FU + cisplatin, within the pivotal phase III (FLAGS) study performed in the target population. Safety profile of S1 in combination with cisplatin was considered manageable and in line with the expected safety

profile of both drugs. The most common side effects are anaemia, neutropenia, vomiting, diarrhoea, abdominal pain, weight decrease, anorexia and fatigue. The most common severe adverse reactions were neutropenia, anaemia, and fatigue.

The combination S1-cisplatin appeared to be better tolerated than 5FU-cisplatin, with lower incidence of gastrointestinal toxicity, particularly stomatitis and mucosal inflammation, probably related to S1 administration, and less haematologic and renal toxicity which were probably related to the lower dose of cisplatin used in the S1 + cisplatin study arm.

Uncertainty in the knowledge about the unfavourable effects

The safety data in support of the combination S1-Oxaliplatin are based on two phase I dose-finding studies (TPU-S1119 and TPU-S1109) where the combination S1 + oxaliplatin + epirubicin and S1 + oxaliplatin + bevacizumab, respectively, were evaluated in patients with advanced solid tumours. Data are considered too scarce to adequately evaluate the toxicity of the S1-oxaliplatin combinations in the proposed target population.

Patients enrolled in the TPU-S1119 study were required to have adequate left ventricular ejection fraction at baseline. According to the study protocol, Echocardiogram, ECG and evaluation of cardiac enzymes were regularly performed in patients enrolled in the study. The MAH should clarify whether reductions of left ventricular ejection fraction or other cardiac adverse events/significant abnormalities were observed in the patients treated and whether such findings should result into inclusion of a warning over this issue in the SmPC.

No safety data have been provided over S-1 in combination with carboplatin (another clinically used platinum compound).

Benefit-risk balance

The positive benefit/risk ratio of the combination S1-cisplatin in the target population has been adequately demonstrated within the original MAA for S1 (Teysuno®), leading to a positive CHMP opinion.

No data have been provided regarding the efficacy and safety of S1 in combination with carboplatin, another clinically used platinum-compound, in the target population. Although no pharmacokinetic interactions have been reported regarding the combination of S-1 and oxaliplatin in the small Caucasian studies reported, data available at this time are too scarce to allow a compelling evaluation of the benefit/risk ratio of S1+platinum-combination regimens other than cisplatin in the proposed target population. No PK data have been provided regarding potential PK interactions between S1, oxaliplatin and epirubicin.

In view of the different pharmacological characteristics, mechanism of action, dosing regimen and toxicity of the different platinum compounds available to date (cisplatin, oxaliplatin, carboplatin), clear demonstration should be provided that the use of platinum compounds other than cisplatin, in combination with S1, will not affect efficacy and safety of the combination and therefore the benefit/risk ratio in the proposed target population. Indeed, extrapolation of the known efficacy and safety results of 5FU/capecitabine in combination with platinum regimens in the target population to S-1 is not considered appropriate.

4. Recommendations

The type II variation in order to change the wording of indication of Teysuno for the treatment of patients with advanced gastric cancer in "**combination with platinum regimens"**, instead of "in combination with cisplatin" as stated by the currently approved indication, is not approvable since major objections and other concerns have been identified, which preclude a recommendation at the present time. The details of these major objections and other concerns are provided in Annex 1 (RSI 1) and should be addressed in writing.

5. Request for Supplementary Information

1. Non clinical aspects

Major objections

Other concerns

Environmental Risk Assessment:

1. The applicant is asked to provide suitable information to verify that an increase in environmental exposure of the active ingredient is not to be expected. If acceptable information cannot be provided, the applicant is asked to submit an updated / revised environmental risk assessment according to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006).

2. Clinical Aspects

2.1 Efficacy and Safety

Major Objections

2. Data available at this time are too scarce to allow a compelling evaluation of the benefit/risk ratio of S1 in combination with platinum-based combinations other than cisplatin in the proposed target population. Very limited data are available over the combination Oxaliplatin-S1 and no data have been provided over the combination carboplatin-S1. In view of the different pharmacological characteristics, mechanism of action, dosing regimen and toxicity of the different platinum compounds available to date (cisplatin, oxaliplatin, carboplatin), clear demonstration should be provided that the use of platinum compounds other than cisplatin, in combination with S1 will not affect efficacy and safety of the combination and therefore the benefit/risk ratio in the proposed target population.

Other concerns

3. Pharmacokinetic characteristics of the three platinum compounds are not identical and moreover the dosing regimen (dose and frequency) is different. Therefore, the applicant is requested to submit data supporting the various combinations with S-1.
4. The MAH is requested to submit the study report of trial TPU-S1109.
5. Patients enrolled in the TPU-S1119 study were required to have adequate left ventricular ejection fraction at baseline. According to the study protocol, Echocardiogram, ECG and

evaluation of cardiac enzymes were regularly performed in patients enrolled in the study. The MAH should clarify whether reductions of left ventricular ejection fraction or other cardiac adverse events/significant abnormalities were observed in the patients treated and whether such findings should result to inclusion of a warning over this issue in the SmPC.

2.3 RMP

Major Objections

Other concerns

6. The term "platinum-based regimens" is considered too generic as this implies that it would also include carboplatin based regimens. The MAH should make it clear throughout the RMP that treatment with Teysuno only includes cisplatin or oxaliplatin.

7. In the RMP information from the published phase III study (Higushi et. al) is used to classify and describe several safety concerns. However, the full article, or any other reports detailing the study and the results could not be located in the submission. The MAH should provide this.

8. It would seem that the data on combination Teysuno + oxaliplatin is from mostly Asians and only few Caucasians. This could be considered a limitation as there are some racial differences between de Asian and Caucasian population (metabolism) that could have an influence on the extrapolation of the safety data and could have an effect on the RMP. The MAH should comment.

9. It is noted that patients enrolled in study S1119 were required to have adequate left ventricular ejection fraction at baseline. Echocardiogram, ECG and evaluation of cardiac enzymes were regularly performed in patients enrolled in the study. In the Clinical AR for this variation a clarification on this is requested. The MAH should discuss whether this information from study S1119 has an impact on the RMP as well.

10. In Part II Module SIV and Module SVII of the RMP very little information is included on the proposed combination of Teysuno and oxaliplatin. In Module SVII.3 mostly only the frequency is added, but other paragraphs in the tables have not been amended and thus only reflect information for the combination with cisplatin. The MAH should update the RMP to include more detailed information, or should better reflect the fact that only limited information is available for the combination with oxaliplatin.

11. In the RMP it is stated that in the Phase III study 8.6% of the patients treated with experienced increased blood creatinine. Information should be provided by the MAH on whether any other AEs suggestive of renal toxicity were reported in the Higuchi study besides blood creatinine increased.
    Even though it is shown in Table 16 of the RMP that increased blood creatinine was reported in substantial more patients receiving the combination with cisplatin (38.8%), it would seem that the combination with oxaliplatin might have an effect on renal function as well. The MAH should comment.

12. In the RMP 'hearing impairment' is mentioned by the MAH as an identified risk specifically for the treatment with cisplatin. Hearing impairment is, however, also associated with oxaliplatin (SmPC lists 'ototoxicity', 'deafness'). Also, for oxaliplatin (and cisplatin) neurotoxicity is a known risk. No mention is made in the RMP on this possible complication with oxaliplatin. The

MAH should discuss whether information on hearing impairment and neurotoxicity for the combination therapy with oxaliplatin should be added to Module SVII.3 of RMP as risks for the combination therapy.

13. The Public Summary should be written with a lay audience in mind. In the Public Summary as presented by the MAH several medical/scientific terms are included that might not be readily understood. Only after an explanation has been provided of these terms can they be used throughout the Public Summary. For instance, the sentence “A fluoropyrimidine and a platinum salt are commonly used and may be associated with an anthracycline or a taxane” in Part VI section 2.1 is considered too difficult without clarification. The MAH is requested to review sections 2.1, 2.2, 2.3 and 2.4.