Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for trifluridine / tipiracil

Proprietary Product Name: Lonsurf and Orcantas

Sponsor: Servier Laboratories Australia Pty Ltd

First round report: July 2016

Second round report: January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words (Information redacted), where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

List of abbreviations

Abbreviations	Meaning
AE	Adverse event
AT	As treated (population)
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BD	Twice daily
BSA	Body surface area
BSC	Best supportive care
CER	Clinical evaluation report
CI	Confidence interval
CL/F	Apparent oral clearance
Cmax	Maximum plasma concentration
CR	Complete response
CRC	Colorectal Cancer
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency

Abbreviations	Meaning
FAS	Full analysis set
FDA	Food and Drug Administration
FTD	Trifluridine
FTY	5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione
GCP	Good clinical Practice
G-CSF	Granulocyte colony stimulating factor
HPLC	High performance liquid chromatography
HR	Hazard ratio
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OCT2	Organic cation transporter-2
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PS	Performance status
PT	Preferred term
QC	Quality Control
QD	Once daily
QTc	QT interval corrected for heart rate

Abbreviations	Meaning
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
TDS	Three times daily
T1/2	Terminal elimination half-life
TK1	Thymidine kinase 1
Tmax	Time of maximum observed plasma concentration
Tpase	Thymidine phosphorylase
TPI	Tipiracil hydrochloride
TR	Tumour response (evaluable population)
TTF	Time to treatment failure
VEGF	Vascular endothelial growth factor

1. Introduction

This is a submission to register a new chemical entity (NCE) fixed-dose combination tablet consisting of trifluridine and tipiracil (trade names Lonsurf and Orcantas) for the treatment of metastatic colorectal carcinoma (mCRC).

1.1. Drug class and therapeutic indication

1.1.1. Drug class

Pharmacotherapeutic group: antineoplastic agents, antimetabolites. ATC code: L01BC59. Trifluridine is an antineoplastic thymidine-based nucleoside analog which is incorporated into deoxyribonucleic acid (DNA) in tumour cells following phosphorylation. Tipiracil inhibits degradation of trifluridine by inhibiting thymidine phosphorylase (TPase), resulting in increased systemic exposure to trifluridine when trifluridine and tipiracil are given together.

1.1.2. Proposed indication

The proposed indication is 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.

1.2. Dosage forms and strengths

The submission proposes registration of the following dosage forms and strengths:

- Lonsurf/Orcantas 15/6.14: white, round, biconvex, immediate-release, film-coated tablet consisting of the fixed-dose combination of trifluridine 15 mg and tipiracil hydrochloride 7.065 mg (equivalent to tipiracil 6.14 mg) imprinted with '15' on one side and '102' and '15 mg' on the other side in grey ink. To be taken orally.
- Lonsurf/Orcantas 20/8.19: pale red, round, biconvex, immediate-release, film-coated tablet consisting of the fixed-dose combination of trifluridine 20 mg and tipiracil hydrochloride 9.420 mg (equivalent to tipiracil 8.19 mg) imprinted with '20' on one side and '102' and '20 mg on the other side in grey ink. To be taken orally.

1.3. Dosage and administration

The proposed Product Information (PI) states that the recommended starting dose of Lonsurf/Orcantas in adults is 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28 day cycle as long as benefit is observed or until unacceptable toxicity occurs. The dose is calculated according to body surface area (BSA), rounded to the nearest 5 mg increment. The dosage should not exceed 80 mg/dose. If doses are missed or held, the patient should not make up for missed doses. The PI provides guidelines for dose modification based on individual safety and tolerability relating to both haematologic and non-haematologic toxicities. The PI also includes recommendations for dosage in special populations. The PI specifies that Lonsurf/Orcantas should be taken with a glass of water, within 1 hour after completion of the morning and evening meals.

Comment: The dosage of 35 mg/m^2/dose is based on the trifluridine component of the fixed-dose combination.

2. Clinical rationale

The submission included a clinical rationale (justification) for the proposed fixed-dose combination tablet. The key aspects of the clinical rationale provided by the sponsor are provided below.

Servier is the Australian sponsor of a new fixed dose combination product (FDC) containing a combination of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio 1:0.5 (weight ratio, 1:0.471) to be used in the treatment of metastatic colorectal cancer (mCRC). FTD is an antineoplastic thymidine-based nucleoside analog which is incorporated into deoxyribonucleic acid (DNA) in tumour cells following phosphorylation. TPI inhibits degradation of FTD by inhibiting thymidine phosphorylase (TPase), thus increasing systemic exposure to FTD when FTD and TPI are given together.

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide. In Australia, there were 17,070 projected new cases diagnosed in 2014, with CRC comprising 13.5% of all new cancer cases diagnosed in 2015. In Australia, patients with unresectable mCRC usually die from the disease, with five year overall survival of about 15%. The primary chemotherapy for mCRC is a combined regimen containing a fluoropyrimidine, such as 5-fluoruracil (5-FU) or capecitabine, along with other agents such as leucovorin (LV), irinotecan and oxaliplatin.

In patients who are refractory to fluoropyrimidines, oxaliplatin and irinotecan and biological targeted agents, treatment options are limited, with the only approved agent in Australia, the USA, EU, and other countries, being the small molecule multi-kinase inhibitor, regorafenib. Due to its unique mechanism of action, Lonsurf will offer an additional oral treatment option for patients with mCRC previously treated with, or not considered suitable candidates for current available therapies, a group who currently have few effective therapies available.

Comment: The sponsor's clinical rationale for the submission is considered to be satisfactory.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 6 clinical pharmacology Phase I studies, including pharmacodynamic and pharmacokinetic data
- 1 population pharmacokinetic analysis
- 1 pivotal Phase III efficacy/safety study
- 5 preliminary Phase I dose-finding studies (legacy studies)
- 1 supportive Phase II clinical efficacy and safety study in Japanese patients
- 1 integrated summary of efficacy, 1 integrated summary of safety
- In vitro human biomaterial studies, and in vitro bioanalytical reports

3.2. Paediatric data

The submission did not include paediatric data. No paediatric data were submitted to the EMA or the FDA. The sponsor states that it has a waiver from having to submit a Paediatric Investigation Plan (PIP) in Europe as the proposed indication in that jurisdiction is considered to be a waived condition (that is, adenocarcinoma of the colon and rectum). The sponsor also states that it has a waiver from the FDA from having to submit paediatric studies.

Comment: The absence of paediatric data from the submission to the TGA is considered to be acceptable. The relevant indication is considered to occur almost exclusively in adults.

3.3. Good clinical practice

The sponsor stated that '(a)ll completed and ongoing clinical studies of TAS-102 have been performed in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines'.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

4.1.1. Clinical studies

The PK and tolerability profile of TAS-102 in patients with cancer have been assessed in 11 TAS-102 clinical pharmacology studies. These 11 studies included 5 initial dose-finding Phase I studies (legacy studies) conducted in the United States (US), and 6 Phase I studies providing the key PK data for TAS-102. In addition, the submission also included a population PK study (Study 12DA25). All clinical pharmacology studies were undertaken in patients with advanced solid tumours. There were no clinical pharmacology studies in healthy volunteers, which is acceptable for the investigation of the PK of a cytotoxic compound.

The sponsor stated that the clinical pharmacology program was developed to:

- establish the tolerability of TAS-102 at a dose of 35 mg/m^2 BD in patients with solid tumours;
- demonstrate the effect of tipiracil (TPI) on the PK of trifluridine (FTD);
- establish the relative bioavailability of TAS-102;
- investigate the effect of food on the PK of TAS-102;
- evaluate the QT corrected for heart rate (QTc) prolongation potential of TAS-102; and
- assess the intrinsic and extrinsic factors that might influence the PK of TAS-102 based on a population PK analysis.

4.1.1.1. Key PK clinical studies (6 studies)

The 6 key PK studies are briefly summarised below.

Table 1: Key studies providing pharmacokinetic data.

Study	Purpose	Population	N (PK)	Dose
TPU-TAS 102-104. Phase I	Relative BA	US patients with advanced solid tumours (excluding breast) for which no standard therapy exists. Single-dose PK data.	38	TAS-102 (15, 20 mg) - 60 mg (3 x 20 mg tablets) and oral solution 60 mg/40 mL, single-dose, crossover, 7 day washout, followed by OL extension.
J001-10040010. Phase I.	PK/ initial tolerability/ dose-finding	Japanese patients with confirmed solid tumours responding poorly to standard treatment. Single- and repeat-dose PK data.	21	TAS-102 tablets (15, 20 mg) - escalating doses of 15 (n = 6), 20 (n = 3), 25 (n = 3), 30 (n = 3) and 35 (n = 6) mg/m^2 PO BD, proposed regimen.
J004-10040040. Phase I	Food effect	Japanese patients with solid tumours (excluding gastric cancer). Single-dose PK data.	16	TAS-102 tablets (15, 20 mg) – 2 doses of 35 mg/m^2 PO under fasting and fed conditions, crossover with ≥ 5 day washout, followed by OL extension.

Study	Purpose	Population	N (PK)	Dose
TPU-TAS-102-101. Phase I.	PK/initial tolerability/ RP3D	US patients with refractory mCRC who had received ≥ 2 lines of prior chemotherapy for mCRC. No PK data.	27	TAS-102 tablets (15, 20 mg); 30 mg/m^2 (cohort 1 (n = 3)) or 35 mg/m^2 (cohort 2 (n = 9)) PO BD for 5 days a week with 2 days rest period for 2 weeks, followed by a 14 day rest period, repeated every 4 weeks (sequential cohorts plus expansion cohort (n = 25) at 35 mg/m^2); 28 day cycles continued until discontinuation criterion met.
TPU-TAS-102-102. Phase I	PK/initial tolerability	US patients with solid tumours (excluding breast cancer) for which no standard therapy exists. Single-dose PK data for FTD after TAS-102 and FTD alone.	39	PK (Part 1) data for FTD after TAS-102 and FTD alone after single-dose 35 mg/m^2, followed by OL extension (Part 2).
TPU-TAS-102-103 Phase I	Cardiac safety; PK/PD analysis.	US patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists.	41	TAS -102 (15, 20 mg tablets) – cardiac safety (Cycle 1) single-blind PO placebo dose on Day -1, TAS-102 35 mg/m2 PO BD on Days 1-5 and 8-12 with rest days 13-28, followed by OL extension.

N (PK) Number of subjects with PK evaluable data. Abbreviations: AUC = area under the curve; BA = bioavailability; BD = twice daily; Cmax = maximum concentrations; Conc = concentrations; E-R = exposure-response; FTD = trifluridine; FTY = 5-trifluoromethyluracil; PO = oral administration; PK/PD = pharmacokinetic/pharmacodynamic; RP3D = recommended Phase III dose; OL = open label; mCRC = metastatic colorectal cancer; rd = repeat dose; sd = single-dose; TAS-102 = fixed-dose combination trifluridine and tipiracil; TPI = tipiracil; 5-CU = 5-carboxyuracil.

Initial dose-finding legacy studies (5 studies)

The initial clinical development of TAS-102 included the evaluation of various dose regimens in 5 Phase I studies conducted in the United States (US) in patients with solid tumours (Studies TAS102-9801, TAS102-9802, TAS102-9803, TAS102-9804, and TAS102-9805). As no patient received the proposed dose of TAS-102 (that is, 35 mg/m^2 BD), these 5 initial Phase I studies were referred to in the submission as 'legacy studies.'

Population PK study (12DA25)

The submission included one population PK study(Study 12DA25), which pooled data for trifluridine (FTD) and tipiracil (TPI) obtained from dense sampling from 3, Phase I studies (Studies J001-10040010, TPU-TAS-102-102, TPU-TAS-102-103) and from sparse sampling from the pivotal Phase III study (Study TPU-TAS-102-301; RECOURSE). This study has been reviewed later in this CER, and relevant data from the study has been included the text and accompanying Tables and Figures.

Comment: The data did not include a mass balance study. However, following a request from the CHMP (Day 120 List of Questions), the sponsor submitted a mass balance study to the EMA. The sponsor included a copy this study (Study TPU-TAS-102-108) in the submission. This study has been evaluated in this CER. The data did not include an absolute bioavailability study. However, the sponsor submitted a justification for not undertaking an absolute bioavailability study. This justification is discussed later in this CER.

4.1.2. Human biomaterial studies (in vitro)

In addition to clinical studies, the submission also included a number human biomaterial studies assessing in vitro membrane permeability, blood cell distribution, plasma protein binding, metabolism, and potential drug-drug interactions of the components of TAS-102 and its metabolites. Furthermore, the submission included extensive comment and additional data relating to these studies in Foreign Regulatory Information, provided by the sponsor in response to the

CHMP's Day 120 List of Questions, and Day 180 List of Outstanding Issues. Relevant information reported from these in vitro human biomaterial studies has been incorporated into the body of this CER. However, primary evaluation of these in vitro studies rests with the non-clinical evaluator.

4.1.3. Bioanalytical reports (in vitro)

In addition to clinical studies, the submission also included a number of in vitro validation reports summarising the analytical methods used to assess plasma and urine concentrations of trifluridine (FTD), tipiracil (TPI), and metabolites in plasma and urine. Plasma and urine concentrations of FTD and TPI, along with their metabolites, were determined by validated liquid chromatography tandem mass spectrometry (LC-MS/MS). The dose of TAS-102 was expressed on the basis of the milligram content of FTD, and concentrations of FTD and metabolites were calculated as for the free form. For TPI, the concentrations were measured as the TPI free form, and the measured concentrations were converted to the equivalent of the hydrochloride form before being subjected to PK analysis. The sponsor comments that bioanalytical methods were sensitive, selective, accurate and reproducible. The primary responsibility for evaluation of the in vitro bioanalytical reports rests with the pharmaceutical chemistry evaluator.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries.

4.2.1.1. Trifluridine

The chemical structure of trifluridine is provided below and the physicochemical properties are summarised below. The molecular formula of trifluridine is $C_{10}H_{11}F_3N_2O_5$ and the relative molecular mass is 296.20.

Figure 1: Chemical structure of trifluridine

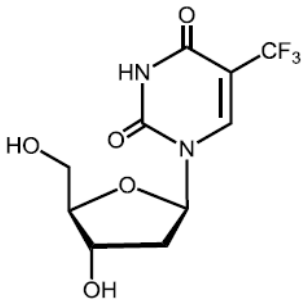


Table 2: Physicochemical properties of trifluridine

Item	Physicochemical Properties
Description	White crystalline powder
Solubility	The solubility in water is 4.45 x 10 mg/mL. The solubility dissolved in Britton-Robinson buffer with various pHs (pH 2 to pH 12) at 20°C is between 44.3 mg/mL and 57.1 mg/mL.
Hygroscopicity	No hygroscopicity of FTD was observed in the water adsorption-desorption isotherm at 25°C, 0% RH – 90% RH.
Melting point	The melting point was 180°C with decomposition.
Thermal analysis	Thermal analysis (TG/DTA and DSC) of FTD was performed. The obtained TG curve and the DTA curve showed endothermic and exothermic peaks

Item	Physicochemical Properties
	accompanied by weight decrease at a temperature range from 170°C to 210°C, which indicates that melting and decomposition of FTD occur simultaneously. The melting point of FTD was calculated to be 190°C from DTA.
UV spectrum	Two wavelengths of maximum absorption between 203 nm and 212 nm, and between 260 nm and 262 nm were observed in ultraviolet-visible (UV-Vis) absorption spectra of FTD for 20 µg/mL solutions of FTD in Britton-Robinson buffer solution in the range pH 2 – pH 12.
Optical rotation	Measured value (specific rotation): +49° (30 mg/mL, water, 25°C and 20°C).
pH	Acidic: pH 4.81 (10 mg/mL, water, at 22.4°C).
Dissociation constant	(p*Ka*) value of FTD was calculated as 8.08 by titration experiment of FTD solution with 1 mol/L hydrochloric acid and with 1 mol/L potassium hydroxide solution.
Partition co-efficient	The 1-octanol/buffer (Britton-Robinson) partition coefficient was measured at 25°C. The partition coefficient remain at about -0.4 from pH 2 to pH 7, while it starts decreasing rapidly after pH 8 due to degradation of the molecule in alkali solution.
Polymorphism	Two crystalline forms, Types I and II.

4.2.1.2. Tipiracil

The chemical structure of tipiracil is provided below and the physicochemical properties are summarised below. The molecular formula of tipiracil is $C_9H_{11}ClN_4O_2$•HCl and the molecular weight of the drug is 279.12.

Figure 2: Chemical structure of tipiracil

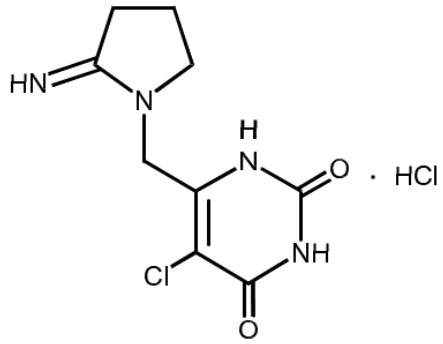


Table 1: Physicochemical properties of tipiracil

Item	Physicochemical Properties
Description	White crystalline powder
Solubility	TPI is very slightly soluble in ethanol, slightly soluble in methanol, practically insoluble in 2-propanol, acetonitrile, acetone, diisopropyl ether and diethyl ether. TPI is soluble in 0.01 M hydrochloric acid and in 0.01 M sodium hydroxide solution.
Hygroscopicity	No hygroscopicity was observed at 25°C between 0% RH and 90% RH.
Melting point	240°C (with decomposition)
Thermal analysis	Endothermic peak and loss in mass associated with melting were observed between 250°C and 280°C.
UV spectrum	Two wavelengths of maximum absorption between 205 nm and 213 nm, and between 277 nm and 301 nm were observed.
Optical rotation	TPI is achiral. Not applicable.
pH	pH 3.74 (10 mg/mL, water)
Dissociation constant	pK_a = 5.95 (titration method)

Comment: The solubility of FTD ranged from 44.3 mg/mL to 57.1 mg/mL in buffer solutions ranging in pH from 2 to 12, and was 44.5 mg/mL in water, 45.1 mg/mL in 1 M HCl, and 47.7 mg/mL in 1 M NaOH, TPI is freely soluble across the pH range 1 to 12, and is soluble in 0.01 M HCL and 0.01 M NaOH. The sponsor reported that both FTD and TPI can regarded as highly soluble drugs, according to the Biopharmaceutics Classification System (BCS).

4.3. Pharmacokinetics in patients with advanced solid tumours

4.3.1. Absorption

4.3.1.1. Sites and mechanisms of absorption

Trifluridine (FTD) and tipiracil (TPI) are both reported to be BCS class III compounds (that is, low permeability, high solubility), based on *in vitro* data reported to show low membrane permeability *in vitro* across Caco-2 cell monolayers (P041295) and high solubility in buffer solutions ranging from 1 to 7.5.

Following a single 35 mg/m^2 dose of TAS-102 administered in the fed state, the median T_{max} values were approximately 2 hours for FTD and 3.5 hours for TPI (TPU-TAS-102-102; TPU-TAS-102-103). The median T_{max} values at steady-state in the fed state were consistent with the values following single-dosing for both FTD (approximately 2.5 hours) and TPI (approximately 3 hours) (TPU-TAS-102-102; TPU-TAS-102-103). The results indicate that both components of TAS-102 are relatively rapidly absorbed following administration in the fed state.

4.4. Bioavailability

4.4.1. Absolute bioavailability

No absolute bioavailability study in humans was submitted. The sponsor submitted a justification for not undertaking such a study. The sponsor commented that when tipiracil (TPI) was administered in combination with trifluridine (FTD) the AUC0-last and Cmax values of FTD were increased by 37-fold and 22-fold, respectively, compared to administration of FTD alone.

Consequently, the sponsor states that as TPI is a PK modulator of FTD with no anti-tumour pharmacological efficacy if TAS-102 is administered IV the change in TPI profile compared to oral administration will 'greatly affect the plasma concentration' of FTD. Therefore, the sponsor concludes that the 'absolute bioavailability value of FTD calculated from oral and intravenous administration of TAS-102 is not informative, and the evaluation of absolute bioavailability of FTD in TAS-102 is technically impossible'. Due to these issues, the sponsor submitted a relative bioavailability study in lieu of an absolute bioavailability study. The sponsor states that in 'accordance with the TGA Guidance, for a new chemical entity such as the fixed dose combination product trifluridine/tipiracil, a relative bioavailability study is acceptable in the absence of an absolute bioavailability study'.

Comment: The sponsor's justification for not submitting an absolute bioavailability study is considered to be acceptable.

4.4.2. Bioavailability relative to an oral solution or micronized suspension

The submission included 1 clinical study assessing the relative bioavailability of TAS-102 tablets (Late CTM formulation) compared to an oral solution (Study TPU-TAS-102-104). In this Phase I study, patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists took single 60 mg doses of TAS-102 (3 x 20 mg tablets) and TAS-102 oral solution following an overnight fast of at least 8 hours in a crossover design with a 7 day washout between doses. In addition to the single-dose cross-over relative bioavailability part of the study (Part 1), the study also included a multiple-dose extension part (Part 2) to assess the safety and anti-tumour activity of TAS-102. Only the results of the relative bioavailability part of the study are reviewed in this section of the CER.

In Part 1 of the study, patients randomised to Sequence A received tablets in Period 1, oral solution in Period 2, and oral solution in Period 3. Patients randomised to Sequence B received oral solution in Period 1, tablets in Period 2, and tablets in Period 3. Blood samples were collected for measurement of plasma and urine concentrations of trifluridine (FTD), tipiracil (TPI), and metabolites of FTD. For both treatment sequences, blood samples were collected on Day 1 of Periods 1, 2, and 3 immediately prior to dosing (0 hour) and at 15 minutes, 30 minutes, 1, 1.5, 2, 4, 6, 8, 10, and 12 hours post-dose.

Of the 46 treated patients, 38 (82.6%) were included in the Crossover BA PK Population, and 45 (97.8%) were included in the All PK population. The Crossover BA PK Population included patients with evaluable PK profiles for at least 2 of the 3 crossover periods, including both tablets and oral solution. In the 38 patients in the Crossover BA PK Population, the median age was 63.5 years (range: 35, 76 years), 55.3% were males, and 89.5% were 'White'. The majority of patients in the Crossover BA PK Population had either colon cancer (36.8%) or pancreatic cancer (26.3%).

21 of the 23 patients randomised to Sequence A and 17 of the 23 patients randomised to Sequence B were included in the Crossover BA PK Population. The most frequent reason for exclusion was inadequate documentation of fasting conditions. Of the 21 patients randomised to Sequence A and included in the Crossover BA PK Population, 19 patients were dosed in all 3 crossover periods (1 tablet and 2 oral solution periods) and 2 patients received 1 tablet and 1 oral solution dose. Of the 17 patients randomised to Sequence B and included in the Crossover BA PK population, 15 patients were dosed in all 3 crossover periods (1 oral solution and 2 tablet periods), and 2 patients received 1 oral solution and 1 tablet dose.

The primary PK endpoints for comparison of TAS-102 tablets and oral solution were the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} of FTD and TPI. The bioavailability of the two formulations was compared using standard statistical methods for the analysis of bioequivalence (that is, analysis of variance (ANOVA)). The two formulations (oral solution and tablets) would be considered to have comparable bioavailability if the 90% CIs of the geometric mean ratios of the $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} values for TAS-102 (experimental treatment) fell within the 0.80 to 1.25 boundary for demonstration of bioequivalence to the oral solution (reference treatment). The results of the relative bioavailability study are summarised below.

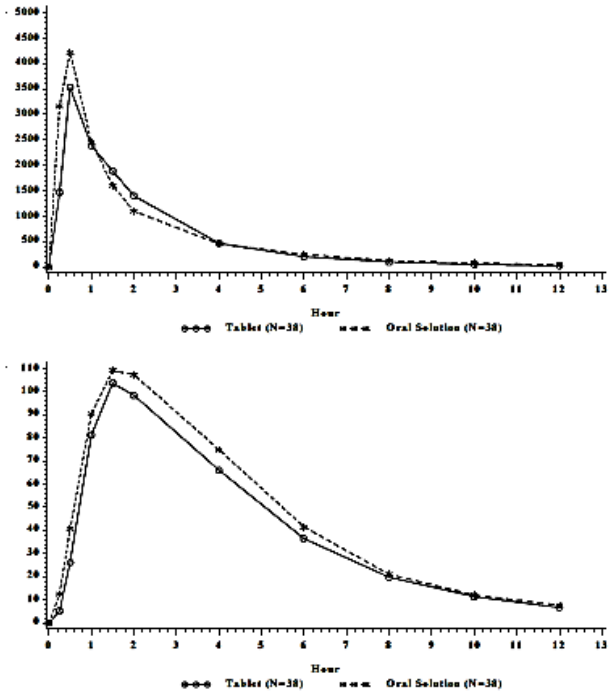
Table 4: TAS-102-104; Relative bioavailability following TAS-102 tablets and oral solution, single 60 mg dose, cross-over BA PK population (n = 38)

Analyte Parameter	Tablet	Oral Solution	Ratio of Geometric Means (Tablet/Oral solution)	
	Geometric Mean[a]	Geometric Mean[a]	Estimate	(90% CI)
Trifluridine (FTD)				
$AUC_{0\text{-last}}$ (ng*hr/mL)	6482.74	6454.59	1.004	(0.926 - 1.089)
C_{max} (ng/mL)	3547.07	4115.58	0.862	(0.786 - 0.945)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	6572.53	6581.22	0.999	(0.918 - 1.087)
Tipiracil (TPI)				
$AUC_{0\text{-last}}$ (ng*hr/mL)	425.39	442.94	0.960	(0.859 - 1.073)
C_{max} (ng/mL)	96.84	95.74	1.012	(0.885 - 1.156)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	448.45	457.82	0.980	(0.865 - 1.109)
5-trifluoromethy uracil (FTY)				
$AUC_{0\text{-last}}$ (ng*hr/mL)	3145.52	3127.11	1.006	(0.959 - 1.055)
C_{max} (ng/mL)	924.74	988.14	0.936	(0.881 - 0.994)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	3226.61	3203.54	1.007	(0.961 - 1.055)
5-carboxy uracil (5-CU)				
$AUC_{0\text{-last}}$ (ng*hr/mL)	12.74	12.35	1.031	(0.921 - 1.154)
C_{max} (ng/mL)	2.36	2.36	1.002	(0.941 - 1.068)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	---b	---b	---	---

a. Derived using the least-square means from the crossover model with replication; b. Could not be determined due to small sample size.

The mean plasma concentration profiles of FTD and TPI are provided below.

Figure 3: Study TPU-TAS-102-104; Plasma concentration profiles for FTD (upper panel) and TPI (lower panel) following single-dose (60 mg) TAS-102 tablet and oral solution



Comment: This was a good quality, single-dose relative bioavailability study. Based on AUC0-last values, the mean relative bioavailability of TAS-102 tablets compared to oral solution was 100% (90% CI: 0.93, 1.09) for FTD and 96% (90% CI: 0.86, 1.07) for TPI. The 90% CIs for AUC0-inf and AUC0-last for the ratio of geometric means (tablet/oral solution) were within the conventional bioequivalence limits of 0.80 to 1.25 for both FTD and TPI. The corresponding 90% CI for Cmax for the ratio of geometric means (tablet/oral solution) of FTD was 0.786 to 0.945, with the mean ratio being 0.862. The result indicates that the absorption of FTD is marginally delayed when administered as a tablet compared to an oral solution. In contrast, the corresponding 90% CI for Cmax for the ratio of geometric means (tablet/oral solution) of TPI was within the conventional bioequivalence limits of 0.8 to 1.25, with the mean ratio being 1.012 (90% CI: 0.885, 1.156). The results indicate that the absorption of TPI is not significantly different for tablet and oral solution formulations. The relative bioavailability for the FTD metabolites, FTY and 5-CU, were similar to that of the parent compound. Overall, the relative bioavailability data suggests that the fixed-dose TAS-102 combination tablet (late CTM formulation) containing FTD and TPI has been optimally formulated.

4.4.3. Bioequivalence of clinical trial and market formulations

The To-be-marketed (TBM) formulation tablets are identical to the Late CTM formulations with the exception of imprinting. The Late CTM formulations were used in Studies TPU-TAS-102-102, TPU-TAS-102-103, TPU-TAS-102-104, and TPU-TAS-102-301 (RECOURSE). The Early CTM formulations were used in Studies J001-10040010, J003-10040030, J004-10040040, and TPU-TAS-102-101.

There were no clinical studies comparing the *in vivo* bioequivalence of the Late CTM, the Early CTM and the TBM formulations. The sponsor stated that the bioequivalence of the formulations was determined by evaluation of their dissolution behaviour. The sponsor reported that the differences between the Early CTM and the Late CTM Formulations (both 15 mg and 20 mg strengths) had no effect on dissolution behaviour under standard dissolution conditions and in a range of buffer solutions with physiologically-relevant pH values. The sponsor stated that the Late CTM and TBM Formulations differ only in the use of trace quantities of ink for imprinting for the proposed TBM

Formulation. Consequently, the sponsor concludes that the dissolution characteristics of the TBM Formulation are not likely to differ from those of the Early CTM or Late CTM Formulations.

Based on the above considerations, the sponsor maintains that the in vivo performance of the TBM Formulation tablets and the Early CTM and Late CTM tablet formulations used in the TAS-102 development program are expected to be sufficiently comparable to allow direct comparison of the PK, efficacy and safety data obtained across all studies in the development program. In addition, the similarity of the in vitro performance of the two formulations allows the in vivo performance of the proposed TBM Formulation to be predicted and supports the proposed dose range and dosing regimen for TAS-102 for the proposed indication.

Comment: The dissolution data have been examined and demonstrate that both the Early CTM and the Late CTM Formulations showed rapid dissolution (≥ 85% dissolved in 15 minutes) in water and buffered media of pH 1.2 to 6.8 at 37oC. In addition, the 20 mg strength of the Late CTM Formulation also showed similar rapid dissolution in FaSSIF (fasted state simulated intestinal fluid, pH 6.5) and FeSSIF (fed state simulated intestinal fluid, pH 5.0) solutions, which are stated by the sponsor to be 'biorelevant' media simulating the fasted and fed states of the small intestine in humans. In addition, the dissolution profiles of the Late CTM and TBM formulations (both 15 mg and 20 mg tablets) showed rapid and comparable dissolution profiles for products manufactured at the development and commercial facilities. Overall, the similarity of the in vitro dissolution data for the relevant formulations support the sponsor's decision not to submit a clinical study comparing the TBM formulation to the Early and Late CTM formulations. However, definitive evaluation of the in vitro dissolution data is a matter for the pharmaceutical chemistry evaluator.

4.4.4. Bioequivalence of different dosage forms and strengths

There were no studies comparing the in vivo bioequivalence of the two proposed tablet strengths of TAS-102 (that is, trifluridine 15 mg/tipiracil 6.14 mg and trifluridine 20 mg/tipiracil 8.19 mg).

Comment: The sponsor stated that the bioequivalence of the two TAS-102 tablet strengths was determined by evaluation of their dissolution behaviour. Examination of the dissolution profiles for the 15 mg and 20 mg tablets are similar for the Early CTM and Late CTM formulations (that is, rapid dissolution ≥ 15% dissolved in 15 minutes) in water and buffered media of pH 1.2 to 6.8 at 37oC. The Late CTM and the TBM formulations differed only in the use of ink imprinting the TBM formulation. Overall, the in vitro dissolution data support the sponsor's decision not to submit a clinical study comparing the bioequivalence of the TBM TAS-102 formulation at the 15 mg and 20 mg strengths. However, definitive evaluation the sponsor's justification is a matter for the pharmaceutical chemistry evaluator.

4.4.5. Influence of food

The effect of food on the PK of trifluridine (FTD) and tipiracil (TPI) was studied in Japanese patients (n = 16) with solid tumours (excluding those with a history of gastric cancer or gastrectomy) (Study J004-10040040). In this randomised, crossover, open-label, Phase I study, patients were given a single 35 mg/m^2 dose of TAS-102 in the fed and fasted states, with a washout period of at least 4 days between the two treatments. The TAS-102 tablets were Early CTM formulations. The meal was high-fat based on FDA guidance and the required number of calories was adjusted according to the mean body weight ratio between US and Japanese patients. Following the single-dose food effect part of the study, patients were permitted to enter a continuous administration part during which the efficacy and the safety of TAS-102 were evaluated.

Food effects were assessed using an ANOVA to calculate the geometric mean ratio (fed/fasting) and associated 90% CI for Cmax, AUC0-12h, and AUC0-inf. In addition, food effects on Tmax were assessed by the Wilcoxon signed-rank test. Blood samples were collected up to 12 hours post-dose (15 and 30 minutes, 1, 2, 4, 6, 8 and 12 hours). There were 16 patients enrolled in the study, but 2 patients were excluded from the evaluation of the food effect part of the study as both ate during

the fasting period. The median age of the 16 PK evaluable patients, 9 males and 7 females, was 62.0 years (range: 37, 73 years), with a median body surface area of 1.5 m^2 (range: 1.4, 1.8 m^2). Twelve patients (75.0%) had a PS score of 0, and 4 (25.0%) had a PS score of 1. At the time of enrollment, 13 patients (81.3%) had complicated disease and 12 (75.0%) were using a concomitant medicine. The most common sites for the primary cancer were the rectum (31.3%), lung (31.3%), and breast (12.5%).
The results for the Cmax and AUC values of interest are summarised below. The median Tmax for FTD in both the fasting and fed states was 1.0 hour, and the median Tmax for TPI was 2 hours in both the fasting and fed state.

Table 5: Study J004-10040040; PK of TAS-102 in the fed and fasted state

PK Parameter	FTD – Geometric Mean Ratio (Fed/Fasting)	TPI - Geometric Mean Ratio (Fed/Fasting)
Cmax	0.6074 (90% CI: 0.5037, 0.7323)	0.5778 (95% CI: 0.4372, 0.6576)
AUC0-12h	0.9560 (90% CI: 0.8566, 1.0670)	0.5526 (95% CI: 0.4802, 0.6358)
AUC0-inf	0.9559 (90% CI: 0.8556, 1.0680)	0.5581 (95% CI: 0.4802, 0.6392)

The safety of TAS-102 was evaluated during the PK Part of the study in 16 subjects. 6 out of the 16 patients treated with TAS-102 experienced adverse events, which were all Grade 1 or Grade 2 in severity. The AEs by preferred term were nausea, pyrexia, monocyte count decreased, neutrophil count decreased, decreased appetite, back pain, headache, cough, productive cough, and rhinitis allergic in 1 patient each. Adverse drug reactions occurred in 2 out of 16 patients treated with the study drug, and were Grade 1 or Grade 2 in severity. The adverse reactions by preferred terms were nausea, monocyte count, and decreased neutrophil count in 1 patient, and headache in 1 patient. No deaths or serious adverse events occurred during the PK Part of the study, and no patient was withdrawn from the study due to an adverse event. No clinically significant changes were observed in laboratory test results or vital signs in either the fed or fasted state.

Comment: This was a good quality study investigating the effect of food on the PK of TAS-102. The study showed that food did not significantly affect the AUC of FTD, but reduced the Cmax of FTD and the Cmax and AUC of TPI by about 40% to 45%. The 90% CIs of the geometric mean ratios (fed/fasting) of AUC for FTD were within the range of 0.80 to 1.25, which is the accepted range for demonstration of bioequivalence. The similar AUC values of FTD in the fed and fasted state suggests that efficacy of TAS-102 is unlikely to be significantly affected by administration with or without food. However, a significant correlation was observed between increased Cmax of FTD and decreased neutrophil count in the TAS-102 dose-finding study conducted in Japanese patients (Study J001-10040010). This observation suggests that TAS-102 should be administered with food, as the Cmax of FTD in the fed state was lower than in the fasting state.

4.4.6. Dose proportionality

In Study J001-10040010, dose proportionality of five escalating TAS-102 dose levels were evaluated in Japanese patients with confirmed solid tumours responding poorly to treatment. The doses of interest were 15 mg/m^2 BD (n = 6), 20 mg/m^2 BD (n = 3), 25 mg/m^2 BD (n = 3), 30 mg/m^2 BD (n = 3), and 35 mg/m^2 BD (n = 6). TAS-102 was administered orally for 5 days a week with 2 days rest for 2 weeks, followed by a 14 day rest (1 treatment cycle), repeated every 4 weeks. Serial blood samples were collected for PK evaluation before and after TAS-102 dosing on Days 1 and 12, and before dosing on Day 5. Urine samples were collected before dosing and at 10 hours post-dose on Day 1.

Linearity was evaluated in a linear regression analysis exploring the relationship between plasma Cmax, AUC0-10h and AUCinf of FTD and TPI on Day 1. The five patients assigned to the dose level of 30 mg/m^2/day were given 20 mg of TAS-102 in the morning, which means that their total daily

dose was 50 mg rather than 60 mg. In these patients, a dose of 24 mg/m^2 per day was used for the analysis.

The results of the linear regression for FTD are shown below. The lack of fit (LOF) of the model was not significant for each of the parameters, indicating that the model is valid. The slope of the three parameters was significant indicating that the parameters increase with dose. However, the intercept for AUC0-10h was statistically significant, with the 95% CI excluding zero, while the intercepts for Cmax and AUCinf were not statistically significant with the 95% CIs including zero. Therefore, it can be concluded that AUC0-10h demonstrates non-linearity, while linearity for Cmax and AUCinf were confirmed. Examination of the results for the linear regression analysis for TPI confirmed linearity for Cmax, AUC0-10h and AUCinf.

Table 6: Results of linear regression analysis for trifluridine in plasma on Day 1

Parameter	R^2	Intercept			Slope			LOF p-value
		estimate	95%CI	p-value	estimate	95%CI	p-value	
C_{max}	0.623	-355	~ 734	0.503	5 35.3	~ 77.4	< 0.0001	0.666
AUC_{0-10h}	0.818	-1910	~ -117	0.0382	1 117	~ 188	< 0.0001	0.262
AUC_{inf}	0.793	-1830	~ 193	0.0735	1 113	~ 190	< 0.0001	0.259

Y = aX+b under the following conditions: X = dose and Y= PK parameter (Cmax, AUC). 95% CI = 95% confidence interval of estimated parameter. Five of the six patients assigned to the dose level of 30 mg/m2/day (AUCinf of FTD obtained from 4/5 cases, no available value in one case) were actually given TAS-102 in the morning in a dose lower than a half of daily dosage by 20%. Therefore, their data were analysed as those obtained from the patients that were given TAS-102 in a dose of 24 mg/m2/day.

The result of the regression analysis using the power model of FTD showed that LOF was not significant for Cmax and AUC, indicating that the analysis was valid. The 95% CI of β for Cmax included 1, while the 95% CIs for the AUC parameters excluded 1. Therefore, the results indicate that the AUC parameters of FTD can be characterised as non-linear. Examination of the results for the analysis of linearity of TPI in plasma using the power model confirmed the linearity of Cmax, AUC0-10h and AUCinf.

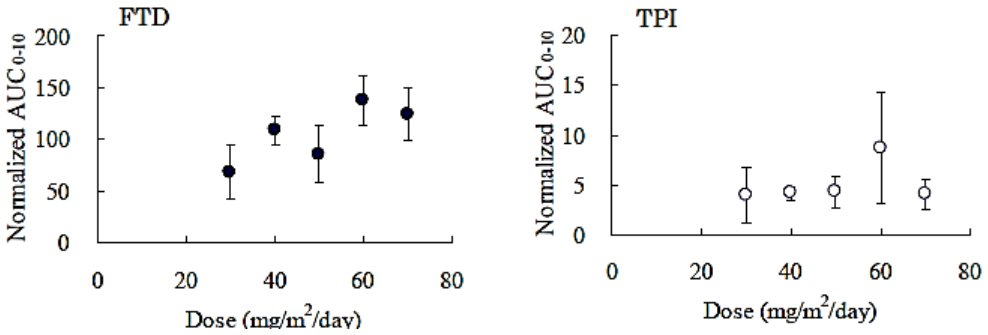
Table 7: Results of analyses of linearity of trifluridine in plasma using power models.

Parameter	R^2	Proportionality coefficient, β			LOF p value
		estimate	95% CI	p-value	
C_{max}	0.697	1.33	0.912 ~ 1.76	< 0.0001	0.775
AUC_{0-10}	0.863	1.47	1.1 ~ 1.76	< 0.0001	0.211
AUC_{inf}	0.846	1.43	1.1 ~ 1.73	< 0.0001	0.201

Y = aX^{β} under the following conditions: X = dose and Y= PK parameter (Cmax, AUC) 95% CI = 95% confidence interval of estimated parameter. Five of the six patients assigned to the Dose Level of 30 mg/m2/day (AUCinf of FTD obtained from 4/5 cases, no available value in one case) were actually given TAS-102 in the morning in a dose lower than a half of daily dosage by 20%. Therefore, their data were analysed as those obtained from the patients that were given TAS-102 in a dose of 24 mg/m^2/day.

Correlation between dose normalised AUC0-10h of FTD and TPI were also undertaken. The results for FTD indicated that AUC0-10h increased more than dose proportionally with increasing dose over the range 30 to 70 mg/m^2/day. However, the dose normalised AUC0-10h for FTD over the dose range 40 to 70 mg/m^2/day was generally constant, with the differences being ≤ 30%, which were similar to the CV values of 12% to 32% at the various dose levels. The results for TPI showed that the AUC0-10h increased proportionally with increasing dose over the dose range 30 to 70 mg/m^2/day. The results are summarised below.

Figure 4: Correlation between the AUC0-10h of FTD and TPI normalised by dose of TAS-1-2 on Day and dosage



Comment: Overall, the data demonstrate that systemic exposure (AUC0-last) to FTD increases more than dose proportionally over the TAS-102 dose range 15 to 35 mg/m2/day, while exposure (Cmax and AUC) to TPI is dose proportional over the dose range.

4.4.7. Bioavailability during single- and multiple-dosing

In Study TPU-TAS-102-102, plasma PK parameters for TAS-102 (trifluridine (FTD), tipiracil (TPI)) and the primary trifluridine metabolite (5-trifuoromethyluracil FTY)) were compared following TAS-102 administered as a single-dose (35 mg/m^2) and multiple-doses (35 mg/m^2 BD) to patients from the USA with advanced solid tumours. The study also examined the effect of TPI on the bioavailability of FTD, which is discussed in the next section of this CER.

Of 44 enrolled patients, 22 were randomised to Group 1 (TAS-102 35 mg/m^2 administered in the morning of Day 1, Cycle 1), and 22 were randomised to Group 2 (FTD 35 mg/m^2 administered in the morning of Day 1, Cycle 1) in the PK Contribution part of the study. There were 38 patients with multiple-dose PK contributing data from at least 1 Cycle, and 7 patients with multiple-dose PK contributing data from 3 Cycles.

In the PK Contribution part of the study (Day 1, Cycle 1), patients randomised to TAS-102 (Group 1) received a single oral dose of TAS-102 (35 mg/m^2) within 30 minutes of the completion of a standardised high-fat, high-calorie breakfast following an overnight fast of at least 8 hours. Blood samples were collected from all patients on Day 1 pre-dose and then post-dose at 15 min, 30 min, 1 h, 1 h 30 min, 2, 3, 4, 6, 8, 10 and 12 h.

In the Extension part of the study, all patients received TAS-102 35 mg/m^2 BD on Days 1 through 5 and Days 8 through 12 of each 28 day cycle. Patients were instructed to take study medication within 1 hour of completion of their morning and evening meal. Blood samples were collected on Day 12 of Cycles 2 and 3 pre-dose (AM), and then post-dose at 30 min, 1, 2, 4, 8, and 12 h. If a patient required a TAS-102 dose reduction then collection of subsequent Day 12 PK blood samples was not required. During the Extension part, patients received TAS-102 treatment until any of the pre-specified treatment discontinuation criteria were met. The results for the single-dose and multiple-dose PK are summarised below.

Table 8: Study TPU-TAS-102-102; Single- and multiple-dose PK of TAS-102 (FTD, TPI) and FTY (primary metabolite of FTD)

Analyte Parameter	Single-dose PK (N = 19)		Multiple-dose PK (At Least 1 Cycle) (N = 38)					
	Cycle 1, Day 1		Cycle 1, Day 12		Cycle 2, Day 12		Cycle 3, Day 12	
	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)
FTD								
$AUC_{0\text{-last}}$	19	7044.53 ±	34	23696.93 ±	25	25056.38 ±	9	26696.38 ±

Analyte Parameter	Single-dose PK (N = 19)		Multiple-dose PK (At Least 1 Cycle) (N = 38)					
	Cycle 1, Day 1		Cycle 1, Day 12		Cycle 2, Day 12		Cycle 3, Day 12	
	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)
(ng*hr/mL)		2411.25 (34.23)		7419.01 (31.31)		10585.99 (42.25)		9218.56 (34.53)
Cmax (ng/mL)	19	2381.21 ± 1047.61 (43.99)	34	4857.06 ± 1930.19 (39.74)	25	5458.00 ± 2269.17 (41.58)	9	5296.67 ± 2291.32 (43.26)
T (hours)[a] max	19	1.50 (0.53, 4.00)	34	1.97 (0.50, 8.00)	25	2.00 (0.50, 4.00)	9	2.00 (1.00, 4.00)
T½ (hours)	19	1.42 ± 0.42	26[b]	2.07 ± 0.43	19[b]	2.10 ± 0.50	5[b]	2.55 ± 0.79
FTY								
AUC0-last (ng*hr/mL)	19	3343.75 ± 897.48 (26.84)	34	5206.27 ± 2055.07 (39.47)	25	5735.54 ± 2344.99 (40.89)	9	5831.50 ± 1938.25 (33.24)
Cmax (ng/mL)	19	764.89 ± 201.44 (26.34)	34	678.76 ± 199.77 (29.43)	25	753.96 ± 205.31 (27.23)	9	782.89 ± 220.20 (28.13)
T (hours) [a] max	19	3.00 (1.00, 6.08)	34	2.00 (0.50, 8.00)	25	2.00 (1.00, 8.00)	9	3.93 (1.03, 4.00)
T½ (hours)	19	1.76 ± 0.38	9[b]	4.51 ± 0.53	6[b]	3.76 ± 0.59	0[b]	-
TPI								
AUC0-last (ng*hr/mL)	19	300.54 ± 126.92 (42.23)	34	372.13 ± 134.71 (36.20)	25	333.07 ± 124.19 (37.29)	9	298.78 ± 91.62 (30.66)
Cmax (ng/mL)	19	68.68 ± 29.71 (43.25)	34	69.35 ± 27.45 (39.58)	25	65.61 ± 25.46 (38.81)	9	53.70 ± 17.05 (31.76)
T (hours) [a] max	19	3.00 (1.02, 8.00)	34	2.01 (1.00, 8.03)	25	3.25 (1.00, 8.00)	9	4.00 (1.97, 4.08)
T½ (hours)	16	2.10 ± 0.47	19[b]	2.40 ± 0.59	12[b]	2.51 ± 0.69	2[b]	2.31 ± 1.03

a. Median (min, max) is presented for Tmax; b. Due to fewer sampling time points on Day 12 (30 min, 1, 2, 4, 8 and 12 hours post-dose), half-life could not be calculated for some patients.

The results of the multiple-dose PK analyses indicate that there is accumulation of FTD between administration of the first dose of TAS-102 (Day 1 of Cycle 1) and after multiple dosing (Day 12 of Cycle 1). Following multiple-dose administration of TAS-102, the AUC0-last for FTD on Day 12 of Cycle 1 (n = 34), Cycle 2 (n = 25) and Cycle 3 (n = 9) was approximately 3-fold higher than after administration on Day 1 of Cycle 1 (n = 19), while the Cmax for FTD was approximately 2-fold higher. The AUC0-last for FTY was also increased after multiple dosing of TAS-102 compared to Day 1, but the Cmax values for FTY were similar after single and multiple dosing. The AUC0-last and the Cmax for TPI were similar after single and multiple dosing of TAS-102.

Comment: The mean ± SD accumulation ratio (Day 12/Day 1) for the AUC0-last for FTD was 3.31 ± 0.77 (CV = 23.3%) for 20 patients with paired data, and 2.16 ± 0.90 (CV = 41.5%) for the

Cmax for FTD. However, it is noted that the t1/2 for FTD was short on both Day 1 and Day 12 of Cycle 1. Therefore, based on the t1/2 values it could be anticipated that FDT should be completely eliminated within 10 to 12 hours of administration. Consequently, the observed accumulation of FTD following repeat BD dosing was unexpected. In additional data presented, the sponsor stated that the mechanism for accumulation of FTD following repeated dosing has not been identified. However, the sponsor stated that accumulation of FTD following repeated dosing will not be a safety risk for the following reasons: (1) the accumulation of FTD based on the AUC is not dose dependent and is predictable (mean accumulation = 2.29 to 2.83 for 15 to 35 mg/m2 BD (J001-10040010)); (2) the inter-individual variation for the accumulation ratio of FTD based on the AUC is relatively small (CV% = 27% (J001-10040010); CV% = 23% (TAS-102-102)); and (3) no further accumulation of FTD with successive cycles of TAS-102 was observed (TAS-102-102)). The sponsor's comments relating to the accumulation of FTD following repeated dosing are considered to be acceptable.

4.4.8. Effect of tipiracil on bioavailability of trifluridine

The effect of tipiracil on the bioavailability of trifluridine was investigated in Study TPU-TAS-102-102. In this study, patients from the USA with solid tumours (excluding breast cancer) for which no standard therapy exists were randomised to receive a single oral dose of TAS-102 containing trifluridine 35 mg/m^2 and tipiracil (Group 1, n = 19) or a single oral dose of trifluridine alone (35 mg/m^2) (Group 2, n = 20) in the morning of Day 1 Cycle 1 (PK part). Serial blood samples were collected within the first 12-hours following dosing.

Based on the ratio of the geometric mean estimates (TAS-102 : FTD), the $AUC_{0\text{-last}}$ for FTD was approximately 37-fold higher following administration of TAS-102 than following administration of FTD alone, and the C_{max} for FTD was approximately 22-fold higher for TAS-102 compared to FTD alone. Plasma concentrations of FTY (the inactive metabolite of FTD) were also lower following administration of TAS-102 compared to FTD alone, due to extensive metabolism of FTD when administered alone. The results for the comparison of geometric mean ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} for FTD and FTY are summarised below, and the mean FTD plasma concentration time-profiles after a single dose of TAS-102 or FTD alone are presented.

Table 9: TPU-TAS-102-102 – Statistical analysis of AUC and Cmax after single-dose of TAS-102 or FTD

	TAS-102		FTD		Ratio of Geometric Mean (TAS-102/FTD)	
Analyte Parameter	**N**	**Geometric Mean**	**N**	**Geometric Mean**	**Estimate**	**(95% CI)**
FTD						
$AUC_{0\text{-last}}$ (ng*hr/mL)	19	6618.07	20	176.27	37.545	(27.56 - 51.15)
C_{max} (ng/mL)	19	2155.17	20	96.24	22.393	(14.19 - 35.34)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	19	6693.97	10[a]	247.88	27.004	(19.56 - 37.27)
FTY						
$AUC_{0\text{-last}}$ (ng*hr/mL)	19	3231.72	20	4121.90	0.784	(0.65 - 0.94)
C_{max} (ng/mL)	19	736.75	20	1104.29	0.667	(0.54 - 0.82)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	19	3320.23	20	4179.31	0.794	(0.66 - 0.96)

a. Due to low and fluctuating plasma FTD concentrations after administration of FTD alone, AUC0-inf could only be determined for 10 patients.

The key PK results for FTD following TAS-102 and FTD alone are summarised below in Table 10. The mean Tmax was approximately 2 hours following administration of both TAS-102 and FTD. The apparent t1/2 for FTD after TAS-102 administration (1.42 hours) was comparable to that observed after FTD administration alone (1.14 hours), while both CL/F and Vd/F for FTD were substantially lower after administration of TAS-102 than after administration of FTD alone.

Table 10: TPU-TAS-102-102 – PK parameters for plasma PK parameters of FTD and FTY after a single-dose of TAS-102 and a single-dose of FTD alone

Analyte Parameter	Mean ± SD (%CV)			
	N	TAS-102	N	FTD Alone
FTD				
$AUC_{0\text{-last}}$ (ng*hr/mL)	19	7044.53 ± 2411.25 (34.23)	20	200.45 ± 95.74 (47.76)
C_{max} (ng/mL)	19	2381.21 ± 1047.61 (43.99)	20	137.79 ± 126.75 (91.99)
T_{max} (hours)[a]	19	1.99 (0.53, 4.00)	20	1.98 ± 1.46 (74.02)
T½ (hours)	19	1.42 ± 0.42 (29.52)	10	1.14 ± 0.55 (48.20)
CL/F (L/hr)	19	10.53 ± 4.46 (42.34)	10	282.90 ± 193.31 (68.33)
Vd/F (L)	19	20.9 ± 9.68 (46.26)	10	486.14 ± 402.88 (82.87)
FTY				
$AUC_{0\text{-last}}$ (ng*hr/mL)	19	3343.75 ± 897.48 (26.84)	20	4280.65 ± 1132.27 (26.45)
C_{max} (ng/mL)	19	764.89 ± 201.44 (26.34)	20	1169.05 ± 402.21 (34.40)
T_{max} (hours)[a]	19	2.69 (1.00, 6.08)	20	2.55 (0.30, 6.00)
T½ (hours)	19	1.76 ± 0.38 (21.49)	20	1.28 ± 0.33 (25.99)

a. Mean (min, max) is presented for Tmax.

Comment: Exposure to FTD was markedly increased when administered in combination with TPI. Exposure to FTY, the primary metabolite of FTD, was marginally lower following TAS-102 compared to FTD alone. The sponsor comments that simple extrapolation based on the AUC values in this study indicates that the dose of FTD alone that would be necessary to achieve the AUC of FTD observed after administration of TAS-102 is 1295 mg/m2 (that is, 35 mg/m^2 x 37) based on BSA. The sponsor noted that this oral dose of FTD is predicted to exceed the projected lethal dose for humans (1194 mg/m^2) based on primate toxicology studies. The equivalent dose in monkeys was reported to be associated with severe gastrointestinal and haematologic toxicities.

Data submitted by the sponsor (D120 Response) suggests that TPI exhibits a maximal inhibitory effect on FTD at TAS-102 dose levels of approximately 20 to 35 mg/m^2, based on the following:

- The inhibitory effect of TPI in the GIT is expected to be maximised due to high concentrations of TPI. The sponsor states that TPI is a high solubility compound with low permeability (Study P041295). The absorption of TPI is relatively poor and is estimated to be 29% as measured from the urinary excretion of TPI (Study TPU-TAS-102-104). Therefore, the GIT is exposed to a high concentration of unabsorbed TPI, which is likely to be much higher than the Ki value of TPI (1.7×10^{-8} M (5 ng/mL)) reported in the literature.[1] The typical Cmax for TPI was estimated to be 69 ng/mL, which is also much higher that the Ki value of TPI, suggesting maximised inhibition of hepatic metabolism of FTD by TPI at the recommended TAS-102 dose level of 35 mg/m^2 BD.
- No clear dose response in endogenous thymidine levels were observed at TAS-102 doses over 30 mg/m^2. The sponsor states that endogenous thymidine level in plasma is a surrogate

biomarker which reflects the inhibitory effect of TPI on the hepatic metabolism of FTD. The plasma concentration of thymidine was measured in the Japanese Study J001-10040010. Inspection of the data indicates no apparent dose response relationship for plasma concentrations of thymidine on Day 1 and Day 12 over the TAS-102 dose range of 30 to 70 mg/m^2 per day, and the Cmax and AUC0-last values appear to plateau at a dose level of 30 mg/mg^2 BD. Therefore, the inhibitory effect of TPI on hepatic metabolism is expected to be maximised at dose levels of 30 mg/m^2 BD or higher.

- Exposure to FTD is generally dose-proportional at the practical dose range (20 to 35 mg/m^2), and there is no irreversible inhibition of TPase by TPI, suggesting that the inhibitory effect of TPI is reaching a plateau at these dose.

4.5. Distribution

4.5.1. Volume of distribution

The apparent volume of distribution (Vd/F) was 21 L (CV=46%) for trifluridine (FTD) and 333 L (CV = 53%) for tipiracil (TPI) after a single 35 mg/m^2 dose of TAS-102 administered under fed conditions (Study TPU-TAS-102-102). The mean Vd/F estimated from the PPK analysis was 10 L for FTD (CV=25%) and 192 L for TPI (CV=63%) (Study 12DA25). In the PPK model, body surface area (BSA) was identified as a significant covariate for the Vd/F of both FTD and TPI. No other tested covariates in the PPK model had a clinically meaningful effect on the Vd/F of FTD or TPI.

4.5.1.1. Plasma protein binding

Trifluridine (FTD) mainly binds to human serum albumin. The *in-vitro* protein binding of FTD in human plasma is greater than 96%, and is independent of drug concentration over the range 0.5 to 50 µg/mL and in the presence of tipiracil (TPI) (Study AE-2350-3G). In the absence of TPI, the percentages of FTD bound in human plasma after incubation with concentrations of 0.5, 5 or 50 µg/mL of FTD were 96.9%, 97.3%, and 96.7%, respectively, and in the presence of TPI (5 µg/mL) the corresponding percentages of bound FTD were 97.0%, 97.0%, and 96.4%, respectively. Plasma protein binding of TPI (0.05, 0.5 and 5 µg/mL) did not exceed 8% in the presence or absence of FTD (50 µg/mL) (Study AE-2350-2G).

In additional data provided, the sponsor stated that the plasma protein binding ratios of ^{14}C-FTD and ^{14}C-FTY were 94.5 ± 0.8% and 77.4 ± 0.9% (mean ± SD of 3 samples) under the same conditions (study 15DB01). Given that the sample for the incubation of ^{14}C-FTY contained 7.26% of ^{14}C-FTD, the plasma protein binding ratio of ^{14}C-FTY would be approximately 70%. The sponsor concluded that both FTD and FTY irreversibly bind to human plasma proteins, including HSA and γ-globulins. In addition, data relating to in vitro induction and inhibition of CYP indicate that the unbound concentration of FTY is unlikely to results in inhibition or induction of CYP enzymes in the clinical setting (Studies XT133055; XT133075). The 50-fold value for the mean unbound Cmax (63.7 µmol/L) for FTY is lower than the maximum FTY concentration (100 µmol/L) used in the CYP inhibition study, and is similar to the maximum FTY concentration (55.5 mmol/L) used in the CYP induction study.

Table 11: PK characteristics of FTY including protein binding and maximum FTY concentrations in the in vitro CYP inhibition and induction studies

Mean Cmax of FTY on Day 1	Protein binding ratio of FTY in human plasma (15DB01)	50-fold the mean unbound FTY Cmax	Maximum FTY concentration in CYP inhibition study (XT133055)	Maximum FTY concentration in CYP induction study (XT133075)
764.89 ng/mL	70%	63.7 µmol/L	100 µmol/L	55.5 µmol/L (10 µg/mL)

4.5.2. Erythrocyte distribution

The blood/plasma concentration ratios for trifluridine (FTD) were 0.611, 0.596, and 0.619 at FTD concentrations of 0.5, 5, and 50 μg/mL, respectively, and the blood/plasma concentration ratios for tipiracil (TPI) were 0.661, 0.598, and 0.581 at TPI concentrations of 10, 100, and 1000 ng/mL, respectively. No concentration dependency for the blood/plasma concentration ratio was observed for either FTD or TPI. The results indicate that in human blood both FTD and TPI are distributed mainly in the plasma fraction.

4.5.3. Tissue distribution

There were no data in humans on tissue distribution.

4.6. Metabolism

4.6.1. Sites of metabolism and mechanisms / enzyme systems involved

The in vitro human biomaterial studies indicate that neither trifluridine (FTD) nor tipiracil (TPI) are metabolised by cytochrome P450 (CYP) enzymes, nor are they inhibitors of these enzymes. The proposed metabolic pathways of FTD and TPI in humans are summarised.

In Study 99C42, it was reported that TPI was not metabolised by CYP enzymes in a human liver S9 preparation, and that TPI had no inhibitory effect on CYP-mediated metabolism of 7-ethoxycoumarin. In study 12DB03, the presence of metabolites of FTD was investigated in vitro following incubation of ^{14}C-FTD with human liver microsomes with or without NADPH and TPI. TPI was added to inhibit any potential metabolism of FTD by thymidine phosphorylase (TPase). The results showed that FTD was not metabolised via CYP pathways in human microsomes.

In study 12DA18, the major metabolite of FTD in vitro was identified as 5-trifluoromethyluracil (FTY), with 5-carboxyuracil (5-CU) and 5-carboxy-2′-deoxyuridine (5-CdUrd) being minor metabolites. The production of 5-CdUrd was also observed when ^{14}C-FTD was incubated with phosphate buffer solution (without human hepatocytes), suggesting that it was also produced by non-enzymatic degradation. Marked inhibition of the metabolism of FTD and thymidine in human hepatocytes was observed in the presence of TPI, indicating that the main route of metabolism of FTD is to FTY, mediated by TPase.

In study 11DA38, the metabolites of FTD in vivo were characterised using a pool of plasma from Japanese patients studied in Study J004-10040040. FTY was the major metabolite detectable in the ultraviolet (UV) chromatogram. FTD was also detected in plasma by the UV chromatogram. In addition, 5-CU and 5-CdUrd were detected in the plasma sample at trace levels. No other metabolites of FTD were detected. In study P05-10408, the metabolites of TPI in vivo were characterised using a pool of plasma and a pool of urine from Japanese patients studied in Study J0004-10040040. Following oral administration of TAS-102 at doses of 30 to 70 mg/m^2/day, concentrations of 6-hydroxymethyluracil (6-HMU) were only quantifiable in plasma at higher doses of TAS-102 (50 to 70 mg/m^2/day). Concentrations of 6-HMU were approximately 1 to 2 ng/mL in plasma and were below the limit of quantification (50 ng/mL) in urine. No other metabolites of TPI were detected.

4.6.2. Total clearance

The mean apparent oral clearance (CL/F) of trifluridine (FTD) based on the final PPK model (study 12DA25) was 2.93 L/hr, with inter-individual variability of 32.2% (CV%). The mean apparent oral clearance (CL/F) of tipiracil (TPI) based on the final PPK model (Study 12DA25) was 88.7 L/hr, with inter-individual variability of 44.3% (CV%). In the PPK model, BSA was identified as a significant covariate for the volume of distribution (Vd/F) of both FTA and TPI. Creatinine clearance (CLcr) was a significant covariate for the clearance (CL/F) of both FTD and TPI, and serum albumin (ALB) was a significant covariate for the CL/F of FTD (negative correlation possibly due to high protein binding of FTD). Other covariates tested had no clinically meaningful impact on

exposure to FTD or TPI (that is, age, sex, race, hepatic function, and concomitant administration of OCT2 inhibitors).

4.6.3. Metabolites identified in humans

4.6.3.1. Active metabolites

No active metabolites have been reported.

4.6.3.2. Other metabolites

See above.

4.6.3.3. Pharmacokinetics of metabolites

The plasma and urinary PK of the major metabolite of trifluridine (5-trifluoromethyluracil (FTY)) were examined in a number of single- and multiple-dose studies. Following a single oral dose of TAS-102 (35 mg/m^2) in the fed state, the Cmax and AUC0-last values of the metabolite FTY were approximately 68% and 51% to 53% lower, respectively, than the parent compound FTD (Studies TPU-TAS-102-102, TPU-TAS-102-103). Following repeat oral doses of TAS-102 (35 mg/m^2 BD) in the fed state, the Cmax and AUC0-last values of metabolite FTY at steady state (Cycle 1, Day 12) were approximately 86% and 78% to 79% lower, respectively, than the parent compound FTD (Studies TPU-TAS-102-102, TPU-TAS-102-103).

4.6.4. Excretion

4.6.4.1. Routes and mechanisms of excretion

The routes of excretion have been determined from the mass balance study (Study TPU-TAS-102-108), and are presented in the next section of this CER.

4.6.4.2. Trifluridine (FTD)

After oral administration of TAS-102 with [14C]-FTD, most of the administered FTD was absorbed and only 2.6% of the dose was excreted unchanged into the feces. The absorbed FTD was metabolised, and the majority of the total radioactivity (TRA) (54.8% of the dose) was excreted into urine as FTY and FTD glucuronide isomers. Only 2.4% of the dose was excreted into expired CO_2, which the sponsor suggests indicates limited ring-opening metabolism of the pyrimidine ring of FTD. Overall recovery of TRA was 59.8% of the dose, which was lower than expected. The sponsor states that this is due to covalent binding of FTD and FTY to plasma or blood proteins. The extractable TRA in the pooled plasma sample consisted of 52.7% FTD and 33.2% FTY. Of note, the extractable fraction of the overall pooled plasma sample was only 6.67%. The major metabolite of FTD in the extractable fraction of plasma and urine was FTY.

Of the dose excreted, the radiochromatogram of the pooled urine sample suggested that TRA in urine consisted of 13.9% unknown front peaks, 45.9% FTY, 33.3% FTD glucuronide isomers, and 2.41% FTD. Given the limited excretion of unchanged FTD into urine, it can be concluded that the major elimination pathway of FTD is via hepatic and/or gastrointestinal metabolism.

4.6.4.3. Tipiracil

After oral administration of TAS-102 with [14C]-TPI, recovered TRA was 76.8% of the dose, which consisted of 27.0% urinary excretion and 49.7% faecal excretion. The sponsor commented that the biliary excretion of unchanged TPI is expected to be negligible based on animal studies in rats. Therefore, the sponsor postulates that the majority of the TRA recovered in the faeces suggests either biliary excretion of TPI metabolites or poor absorption of TPI. Based on TRA derived [14C]-TPI excreted into the faeces and the urine, it can be estimated that the absorbed fraction of TPI is ≥ 27% but < 50% of the administered dose. The radiochromatograms of pooled samples suggested that the plasma TRA consisted of 30.9% 6-HMU and 53.1% TPI, the urine TRA consisted of 14.0% 6-HMU and 79.1% TPI, and the faecal TRA consisted of 34.4% 6-HMU and 48.2% TPI. It was noted that the 6-HMU metabolite appeared in plasma or in blood after disappearance of TPI, which according to the sponsor may suggest that 6-HMU was slowly produced via a metabolic pathway

other than hepatic metabolism. Overall, TPI was the major component and 6-HMU was the major metabolite of TPI in human plasma, urine, and feces. No other metabolites greater than 5.02% TRA were observed from these sources.

4.6.5. Mass balance studies

The Phase I, open label, mass balance Study TPU-TAS-102-108 was finalised on 17 June 2015. The study was undertaken in patients with advanced solid tumours at the University of Pittsburgh Cancer Institute, USA. The first patient was allocated to treatment on 12 May 2014 and the last patient completed the study on 8 September 2014. The study also included an extension part aimed at assessing the safety profile of TAS-102, and the anti-tumour activity of the drug. Only the mass-balance part of the study is discussed below.

The objectives of the mass-balance study were as follows:

- To determine the total recovery and relative excretion of radiocarbon in urine, feces, and expired air after a single dose of TAS-102 with a light tracer dose of [14C]-FTD or [14C]-TPI.
- To evaluate the PK profile of total radioactivity (TRA) in blood and plasma after a single dose of TAS-102 with a light tracer dose of [14C]-FTD or [14C]-TPI.
- To evaluate the metabolic profile of TAS-102 in plasma, urine, and feces following administration of TAS-102 with a light tracer dose of [14C]-FTD or [14C]-TPI using pooled samples.
- To identify major radioactive peaks of metabolites found in metabolite profiling analyses.
- To determine plasma FTD, FTY, and TPI PK parameters following single oral dose administration of TAS-102 with a light tracer dose of [14C]-FTD or [14C]-TPI.

In the mass-balance part of the study, a single 60 mg dose of TAS-102 with radiolabelled FTD or TPI in an oral solution was given, with PK sampling on Day 1 through Day 8. Patients were allocated to 1 of the following 2 treatment groups: Group A received a single dose of 60 mg TAS-102 with a light tracer dose (200 nCi, approximately 1.2 μg) of [14C]-FTD administered as an oral solution on Day 1 in the morning within 30 minutes of completion of a standardised breakfast; and Group B received a single dose of 60 mg TAS-102 with a light tracer dose (1000 nCi, approximately 5.6 μg) of [14C]-TPI administered as an oral solution on Day 1 in the morning within 30 minutes of completion of a standardised breakfast.

The first 4 patients enrolled were allocated to Group A, and the next 4 patients enrolled were allocated to Group B. The data from these 8 patients were included in the PK analysis if complete collection of all urine and faecal samples between 0 and 96 hours post-dose had been obtained, and there had been no more than 1 missing urine or faecal sample between 96 and 168 hours post-dose. Patients remained at the clinical site from 10 hours prior to the administration of study drug on Day 1 through to the completion of all post-dose sample collections on Day 8. During Day 1 through Day 8, samples of whole blood, urine, and feces were collected for measurement of total radioactivity (TRA) after administration of [14C]-FTD or [14C]-TPI in the TAS-102 oral solution.

For both treatment groups, 8.5 mL of blood was collected at pre-dose (0 hour), and then post-dose at 30 min, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours. At each time point, an 0.5 mL subsample of whole blood was retained for accelerator mass spectrometry (AMS) analysis of TRA. The remainder was centrifuged to prepare plasma for determination of FTD, FTY and TPI concentrations by means of conventional analysis using LC-MS/MS, for AMS analysis of TRA, and for metabolite profiling and identification. Urine and faecal samples were collected pre-dose (single sample collection), and post-dose from 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144 and 144 to 168 hours. Samples of carbon dioxide (CO_2) were collected from subjects in Group A for determination of TRA ($^{14}CO_2$) in expired air pre-dose (0 hour), and then post-dose at 30 minutes, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours.

It was planned that 12 patients were to be screened and enrolled in order to obtain 8 patients evaluable for mass-balance analysis (4 in Group A, 4 in Group B). The patients were required to have advanced solid tumours (excluding previously treated breast cancer) for which no standard therapy exists. All patients were to be ≥ 18 years and both males and females could be enrolled. The mass balance part of the study included all 8 enrolled patients, and all 8 patients completed the mass balance analysis. The mean ± SD (median) age of the 8 patients was 57.4 ± 8.57 years (58.0 years), with a range of 45 to 68 years. 6 of the 8 patients were male and 2 were female. All 8 patients were categorised as 'Caucasian/White'. 6 patients had ECOG performance scores of Grade 0 (75%), while 2 patients in Group A (25%) had ECOG scores of Grade 1. 6 patients had colon cancer (75%) and 2 had rectal cancer (25%). The majority of patients had undergone ≥ 4 prior treatment regimens (6 patients, 75%); 1 patient in Group B (12.5%) had undergone 3 prior regimens, and 1 patient in Group A (12.5%) had undergone 2 prior regimens. Overall, the demographics and baseline characteristics of patients in Treatment Group A (n = 4) and Treatment Group B (n = 4) were comparable.

4.6.6. Results; FTD (Group A)

The PK of TRA in plasma and blood for [14C]-FTD are summarised, and the plasma and blood TRA over time are provided. After oral administration of TAS-102 with [14C]-FTD, TRA in both blood and plasma exhibited similar concentration-time profiles with rapid absorption and initial elimination, followed by slow terminal phase elimination. The TRA from [14C]-FTD reached a peak value in whole blood and in plasma within 2 hours, decreasing thereafter and then slowly declined 12 hours after dosing. The TRA blood/plasma ratio of [14C]-FTD was below 1 through the 4-hour time point, and was greater than 1 for the remainder of the sampling time points, reaching approximately 1.4 at the last available sampling point (168 hours). The median T_{max} of TRA in blood occurred at 1.925 hours, while the T_{max} in plasma occurred at 1.442 hours. The median $T_{1/2}$ for TRA in plasma was estimated to be approximately 320 hours, but this value is unreliably as the percent extrapolated AUC was > 20% for all patients. The sponsor stated that the $T_{1/2}$ for TRA in plasma was provided for 'informational purposes', and that the $T_{1/2}$ for TRA in blood could not be calculated 'as it was much longer than the observation period'. The sponsor notes that the $T_{1/2}$ for TRA in plasma of approximately 320 hours was comparable to the known turnover half-life of human serum albumin (approximately 20 days), and suggests that the long $T_{1/2}$ might be due to covalent lysine-specific binding of FTD and FTY to human serum albumin.

The PK of FTD, FTY, and TPI for patients in Group A are summarised. To compare the LC-MS/MS concentration with TRA, FTY concentrations were converted to FTD equivalent concentrations. The mean C_{max} of TRA (3095.0 ng-eq/mL in plasma) was comparable to the sum of FTD C_{max} (1717.5 ng/mL) and FTY C_{max} (948 ng/mL as FTD equivalent). However, the $AUC_{0\text{-last}}$ of TRA in plasma (86248.4 ng-equiv*hr/mL) was approximately 10-fold higher than the sum of $AUC_{0\text{-last}}$ of FTD (6026.1 ng*hr/mL) and FTY (4500 ng*hr/mL as FTD equivalent). Both FTD and FTY in plasma decreased to BLQ levels (< 5 ng/mL) at 24 hours after dosing, suggesting that the TRA in plasma at time points later than 24 hours consists of metabolites of FTD other than FTY. Based on the AUC values, FTD and FTY accounted for approximately 12% of the total AUC of TRA in plasma.

The excretion of TRA from [14C]-FTD in urine, feces, and expired CO_2 are summarised. After oral administration of TAS-102 with [14C]-FTD, most of the administered FTD was absorbed and only 2.6% of the dose was excreted unchanged into the feces. The absorbed FTD was metabolised, and the majority of TRA (54.8% of the dose) was excreted into urine as FTY and FTD glucuronide isomers. Only 2.4% of the dose was excreted into expired CO_2, which the sponsor suggests shows limited ring-opening metabolism of the pyrimidine ring of FTD. Of the dose excreted, the radiochromatogram of the pooled urine sample suggested that the TRA in urine consisted of 13.9% unknown front peaks, 45.9% FTY, 33.3% FTD glucuronide isomers, and 2.41% FTD. Given the limited excretion of FTD into urine, the major elimination pathway of FTD is considered to be via hepatic or gastrointestinal metabolism.

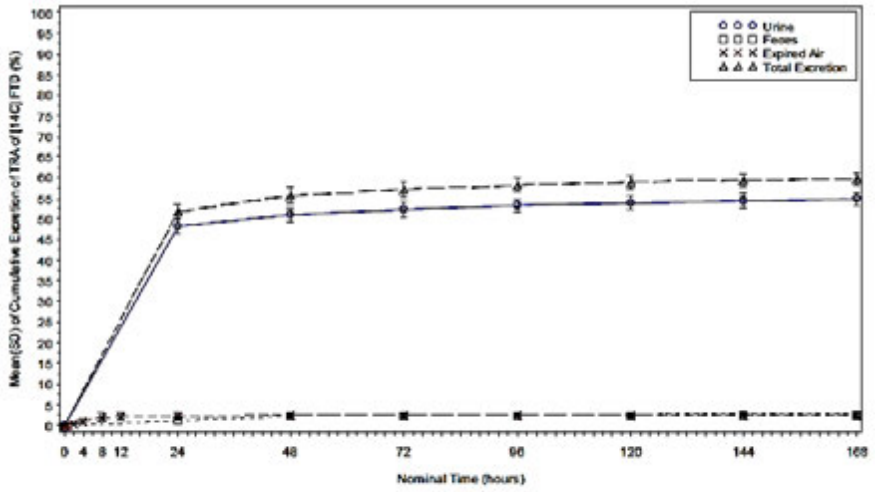
Table 12: TPU-TAS-102-108 - PK parameters for total radioactivity of [14C]-FTD excreted in urine, faeces, respired $^{14}CO_2$ and total recovered, PK Population Group A

	Urine		Feces	Expired CO_2		TRA
	Ae%R (%)	CLr (mL/hr)	Ae%F (%)	$AURC_{0\text{-last}}$ (mg-equivalents)	Ae%CO_2 (%)	Ae%total (%)
	4	4	4	4	4	4
Mean ± SD	54.8 ± 1.7	414.7 ± 134.8	2.6 ± 0.4	1.4 ± 0.5	2.4 ± 0.9	59.8 ± 1.6
%CV	3.2	32.5	14.4	36.9	36.9	2.6
Median	54.2	427.8	2.7	1.3	2.1	59.3
Min - Max	53.4 - 57.3	255.8 – 547.5	2.1 – 3.0	1.0 – 2.2	1.7 – 3.7	58.5 – 62.0

Ae%CO2 = percentage of administered dose excreted as $^{14}CO_2$; Ae%F = percentage of administered dose excreted in feces; Ae%R = percentage of administered dose excreted in urine; Ae%total = Percentage of administered dose recovered from all routes of elimination; AURC0-last = Area under the 14CO2 excretion rate curve from time 0 to the last measurable $^{14}CO_2$ concentration; CLr = Renal clearance; CV = coefficient of variation; FTD = trifluridine; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; TRA = total radioactivity.

The cumulative excretion of TRA derived from [14C]-FTD over the 168-hour sampling period is presented below. The majority of recovered TRA was eliminated from the circulation within the first 24 hours after oral administration of [^{14}C-FTD], with the remaining radioactivity being eliminated much more slowly.

Figure 5: Cumulative excretion of total radioactivity of ^{14}C derived from FTD in urine, feces, and respired CO_2 and total recovered radioactivity, PK population Group A



Mean and Standard Deviation values for Cumulative Excretion of ^{14}C derived from [^{14}C]-FTD in urine, feces, an respired CO_2 for patients in Group A plotted on a linear scale.
Source: Figure 14.4.18.1
FTD = trifluridine; PK = pharmacokinetic; SD = standard deviation; TRA = total radioactivity.

Overall recovery of TRA was 59.8% of the dose, which was lower than expected. Therefore, it can be estimated that approximately 40% of the dose remained in the body at 168 hours after the single-dose of TAS-102. The sponsor stated that, based on the typical total blood volume of 5 L in humans, the amount of TRA in blood could be roughly estimated as 2.6 mg-eq (that is, 520 ng-eq/mL at the 168-hour time point x 5 L). This figure accounted for 4.3% of the total dose administered. Therefore, the sponsor suggests that unrecovered TRA remained not only in blood but also in other proteins in the body.

In the metabolite profiling experiment, the extraction efficiency from plasma samples was measured for the pooled plasma samples at different collection time points. The extraction

recovery from the pooled sample was > 90% at 2 hours after dosing, but declined to < 1% at 96 hours and later time points. Approximately 90% of TRA was bound to plasma protein. In human plasma, TRA extraction efficiency of the overall pooled TRA samples was poor, and the extractable TRA fraction of 6.67% consisted of 52.7% FTD and 33.2% of FTY. The sponsor suggests that approximately 90% of TRA in plasma was not extractable due to covalent binding of TRA to plasma proteins. In urine, excreted TRA consisted of 45.9% FTY, 2.41% FTD, and 33.3% of suspected FTD glucuronide isomers. In faeces, multiple metabolite peaks were observed, but those were present only at trace levels.

4.6.7. Results – TPI (Group B)

The PK of TRA in plasma and blood for [14C]-TPI are summarised, and the plasma and blood TRA over time are provided. TRA (ng-equivalents/mL) from [14C]-TPI reached a peak value in whole blood and in plasma within 2 to 2.5 hours, decreasing thereafter, and then slowly declining 12 hours after dosing. The blood/plasma ratio of [14C] TRA derived from TPI was initially below 1 up to the 4-hour time point, and increased to 1.2 to 1.5 at the 8 hour through 24 hour sampling time points. The median Tmax of TRA in blood and plasma was reached at 2 hours.

The PK of FTD, FTY, and TPI for patients in Group B are summarised. The Cmax of TRA in plasma (54.2 ng-equiv/mL) was comparable to the Cmax of TPI (48.2 ng/mL) measured by LC-MS/MS. However, the AUC0-last of TRA in plasma (677.5 ng-equiv*hr/mL) was approximately 3-fold higher than the AUC0-last of TPI (210.4 ng*hr/mL). Therefore, the majority of TRA at earlier time points consisted of TPI, with the TRA in plasma after 12 hours consisting of slower eliminating TPI metabolites. Based on the AUC values, TPI accounted for approximately 30% of the total AUC of TRA in plasma.

The excretion of TRA from [14C]-TPI in urine and faeces is summarised below. The total cumulative elimination of TRA derived from [14C]-TPI was approximately 76.8% of the administered dose, and consisted of 27.0% urinary excretion and 49.7% faecal excretion.

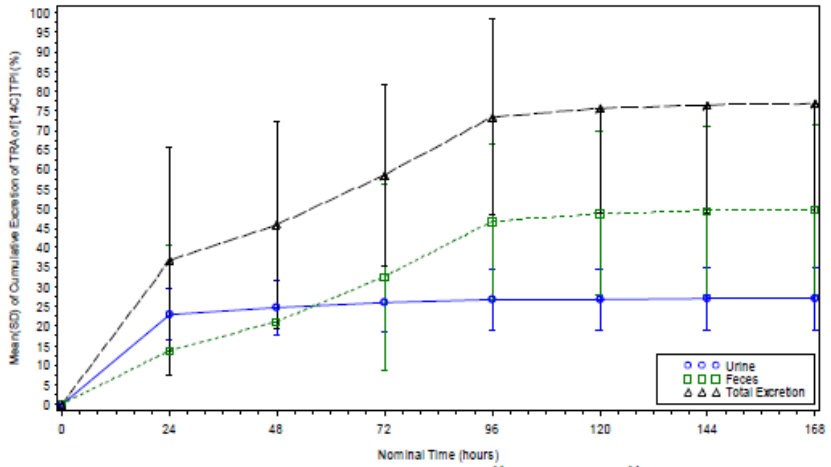
Table 13: Study TPU-TAS-102-108; PK parameters for total radioactivity of [14C]-TPI excreted in urine, faeces, and total recovered, PK Population Group B

	Urine		Feces	TRA
	Ae%R (%)	**CLr (mL/hr)**	**Ae%F (%)**	**Ae%total (%)**
N	4	4	4	4
Mean ± SD	27.037 ± 8.0065	10549.115 ± 3284.9595	49.723 ± 21.5785	76.760 ± 27.6565
%CV	29.6	31.1	43.4	36.0
Median	25.725	10227.874	59.525	86.049
Min - Max	18.80 - 37.90	6916.44 - 14824.27	17.46 - 62.39	36.26 - 98.68

Ae%F = percentage of administered dose excreted in feces; Ae%R = percentage of administered dose excreted in urine; Ae%total = Percentage of administered dose recovered from all routes of elimination; CLr = Renal clearance; CV = coefficient of variation; FTD = trifluridine; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; TRA = total radioactivity.

The cumulative excretion of TRA derived from [14C]-TPI over the 168-hour sampling period is presented below. The majority of the faecal excretion was recovered within 96 hours post-dose, while renal excretion was recovered within 24 hours.

Figure 6: Cumulative excretion of total radioactivity of ^{14}C derived from TPI in urine, faeces, and total recovered radioactivity; PK population Group B



Mean and Standard Deviation values for Cumulative Excretion of ^{14}C derived from [^{14}C]-TPI in urine and feces for patients in Group B, plotted on a linear scale.
Source: Figure 14.4.19.1
PK = pharmacokinetic; SD = standard deviation; TPI = tipiracil hydrochloride; TRA = total radioactivity.

Most of the TRA was extractable from the plasma sample, with the extraction efficiency being 83.5%. The radiochromatogram of the pooled plasma sample suggested that the plasma TRA consisted of 53.1% TPI and 30.9% 6-hydroxymethyluracil (6-HMU). The major metabolite of TPI in plasma was 6-HMU, and no other metabolites greater than 5.02% TRA were identified in human plasma. In the urine sample, TRA consisted of 79.1% TPI and 14.0% 6-HMU. The major metabolite of TPI in urine was 6-HMU, and no other metabolites with concentrations greater than 1.26% TRA were found in human urine. Most of TRA was extractable from the faeces sample, with the extraction efficiency being 106%. The faecal TRA consisted of 48.2% TPI and 34.4% 6-HMU. The major metabolite of TPI in faeces was 6-HMU, and no other metabolite peaks with concentrations greater than 4.09% were found in human faeces. TPI was the major component and 6-HMU was the major metabolite of TPI in human plasma, urine and faeces. No other metabolites greater than 5.02% TRA were observed in these sources.

4.6.8. Renal clearance

In Study TPU-TAS-102-104, urinary excretion of FTD, TPI, FTY, 5-CdUrd, and 5-CU after administration of TAS-102 tablets was evaluated as an exploratory endpoint. On Day 1 of Period 1 (for patients in Sequence A) and Day 1 of Period 2 (for patients in Sequence B), urine samples were collected from all patients for measurement of urinary excretion of TAS-102 components (FTD and TPI) and metabolites of FTD (FTY, 5-CdUrd and 5-CU). Urine samples were collected at the following time intervals relative to dosing (TAS-102 tablets): prior to dosing (0 hour) and from 0 to 12, 12 to 24, and 24 to 48 hours post-dose. Patients were instructed to void prior to dosing. Following a single 60 mg dose of TAS-102, the mean 48 hours cumulative urinary excretion was 1.5% for unchanged trifluridine, 19.2% for FTY (the major metabolite of trifluridine) and 29.3% for unchanged tipiracil. The urinary excretion results are summarised below.

Table 14: Study TPU-TAS-102-104; Urinary excretion of TAS-102 components and FTD metabolites after administration of TAS-102 tablet, all PK population

Analyte	N	Percentage of administered parent dose excreted [a] (mean ± SD)
FTD (unchanged)	36	1.5 ± 1.50 %
FTY	36	19.2 ± 8.28 %
5-CdUrd	36	0.0 ± 0.0
5-CU	36	0.3 ± 0.39 %

Analyte	N	Percentage of administered parent dose excreted [a] (mean ± SD)
Total [b]		21.0 ± 9.07 %
TPI (unchanged)	36	29.3 ± 17.03%

a. Based on molar equivalents; b. Sum of unchanged FTD and its metabolites.

The results for renal clearance of TAS-102 components and FTD metabolites are summarised below.

Table 15: Study TPU-TAS-102-104; Renal clearance of TAS-102 components and FTD metabolites after administration of TAS-102 tablets, all PK population

Parameter, unit	N	Mean ± SD
CLr (FTD), mL/min	37	2.29 ± 3.374
CLr (FTY), mL/min	38	40.85 ± 24.622
CLr (TPI), mL/min	34	292.67 ± 105.650
CLr (5-CdUrd), mL/min	0	-
CLr (5-CU), mL/min	1	133.57
CL_{Cr}, mL/min	38	104.77 ± 42.271
eGFR, mL/min/1.73 m^2	38	84.38 ± 27.766

CLr = renal clearance; CLCR = creatinine clearance; eGFR = estimated glomerular filtration rate.

Comment: The data suggest that urinary excretion is the major route of elimination for TPI, but a minor route of administration for FTD. TPI is mainly eliminated by urinary excretion in humans, because the concentrations of major metabolites of TPI were similar to or below the lower limit of quantification in human plasma and urine, respectively, and the biliary excretion of TPI was reported by the sponsor to be negligible in a rat PK study. Renal tubular secretion is involved in the urinary excretion of TPI because the renal clearance of TPI (292.67 mL/min) is about 3-fold higher than the creatinine clearance (104.77 mL/min).

4.7. Intra- and inter-individual variability of pharmacokinetics

Based on the PK data from patients in Study TPU-TAS-102-104, the inter-subject variability (CV %) for trifluridine was 64% for Cmax and 61% for AUC0-last, and the corresponding results for intra-subject variability were 25% and 16%. The inter-subject variability (CV %) for tipiracil was 59% for Cmax and 54% for AUC0-last and the corresponding results for intra-subject variability were 36% and 30%. The results are summarised below.

Table 16: Study TPU-TAS-102-104; Assessment of inter-subject and intra-subject variability in FTD and TPI following administration of TAS-102

	AUC0-last	Cmax
FTD		
Between subject (inter-subject) variance	15563809.7	5200940.8
Within subject (intra-subject) variance	1126848.2	808638.0
Geometric mean	6482.7	3547.1
Inter-subject CV(%)	60.9	64.3
Intra-subject CV(%)	16.4	25.4

TPI		
Between subject (inter-subject) variance	53301.4	3225.5
Within subject (intra-subject) variance	15124.3	1212.6
Geometric mean	425.4	96.8
Inter-subject CV(%)	54.3	58.6
Intra-subject CV(%)	28.9	36.0

AUC units are ng*hr/mL; Cmax units are ng/mL. CV: Coefficient of variation. These are overall estimates based on the analysis of log-transformed data from TPU-TAS-102-104, from the tablet estimates from the GLM model for the cross-over design with replication.

Comment: Intersubject variability of Cmax and AUC0-last was high for both FTD and TPI following administration of TAS-102. The intra-subject variability of Cmax and AUC0-last for FTD was < 30% for both parameters, which the sponsor categorises as low variability.

4.8. Population PK analysis

The submission included a population PK analysis (12DA205) for FTD and TDI following TAS-102 administration using the combined PK data from three Phase I Studies J001-10040010, TPU-TAS-102-102, TPU-TAS-102-103, and sparse sampling PK data from the pivotal Phase III efficacy and study (RECOURSE). The studies contributing data to the population PK analysis are summarised.

The objectives of the analysis were:

- To establish the population PK parameters of FTD and TPI, and to determine significant intrinsic and extrinsic factors that influence drug exposure; and
- To estimate the individual drug exposures in patients enrolled in the Phase III study (RECOURSE) using the established population PK parameters.

The principal analytical technique was the population PK approach using nonlinear mixed effect modelling (NONMEM). A compartment model was applied for FTD and TPI as the structural model, and subject demographics, clinical laboratory parameters and other subject background information were used in the covariate modelling to assess and incorporate their effects on the individual PK parameters. The performance of the final model was verified using standard model validation procedures. The reporting of the study was consistent with the relevant TGA adopted guideline (Guideline on Reporting the Results of Population Pharmacokinetic Analysis). The plasma concentration data used in the analysis are summarised below.

Table 17: Population PK analysis (12DA25); Summary of the plasma concentration data analysed

Study	Number of individuals	Number of concentration data	Number of concentration data excluded	Number of individuals analyzed	Number of concentration data analyzed
TPU-TAS-102-301	139	832	6	138	826
TPU-TAS-102-102	39	546	2	39	544
TPU-TAS-102-103	42	812	6	41	806
J001-10040010	21	378	0	21	378
Total	241	2568	14	239	2554

4.8.1. Results

- The structural model for trifluridine was a 1-compartment disposition model with transit absorption model (4 transit compartments). A covariance structure for the inter-individual variability (IIV) between Vd/F and CL/F was included in the base and final model.
- The structural model for tipiracil was a two-compartment disposition model with transit absorption model (4 transit compartments). A covariance structure for the inter-individual (IIV) between Vd/F and CL/F was included in the base and final model.
- The final model parameters estimated for FTD are summarised, and the final model parameters for TPI are summarised. No single-dose data were included in the model.
- The population mean apparent volume of distribution (Vd/F) for FTD was 10.L (CV% = 25.3) at median BSA of 1.81 m^2. The model showed that Vd/F increased with increasing BSA. Inclusion of BSA as a covariate of Vd/F reduced the inter-individual variability (CV%) of Vd/F from 30.8% in the base model to 25.3% in the final model. Apart from BSA, no other covariates significantly affected the Vd/F of FTD.
- The population mean apparent clearance (CL/F) for FTD was 2.93 L/hr at a median creatinine clearance (CLCR) of 103 mL/min and a median serum albumin (ALB) of 3.9 g/dL. The model showed that CL/F increased with increasing CLCR, and decreased with increasing ALB. Inclusion of CLCR and ALB as covariates of CL/F reduced the inter-individual variation (CV%) of CL/F from 39.2% in the base model to 32.2% in the final model. Apart from CLCR and ALB, no other covariates significantly affected the CL/F of FTD.
- The population mean Vd/F for TPI was 192 L at a median BSA of 1.81 m^2. The model showed that Vd/F increased with increasing BSA. Inclusion of BSA as a covariate of Vd/F reduced the inter-individual variability (CV%) of Vd/F from 65.0% in the base model to 62.7% in the final model. Apart from BSA, no other covariates significantly affected the Vd/F of TPI.
- The population mean apparent clearance (CL/F) for TPI was 88.7 L/hr at a median creatinine clearance (CLCR) of 103 mL/min. The model showed that CL/F increased with increasing CLCR. Inclusion of CLCR as a covariate of CL/F reduced the inter-individual variation (CV%) of CL/F from 50.2% in the base model to 44.3% in the final model. Apart from CLCR, no other covariates significantly affected the CL/F of TPI.

Comment: BSA was a significant covariate for Vd/F in both final models of FTD and TPI. Race and gender were not included in the final models. Therefore, given that these two factors can affect BSA it is possible that they are confounders of the association between BSA and Vd/F in the final models. However, adjusting for dose based on BSA should account for differences in the parameter due to race and gender.

4.9. Pharmacokinetics in special populations

4.9.1. Pharmacokinetics in subjects with impaired hepatic function

No dedicated clinical studies evaluating the effect of hepatic impairment on the PK of TAS-102 were submitted. In the population PK analysis (12DA25), hepatic function parameters (ALT, AST, ALP and bilirubin) were not significant covariates for the PK parameters (including CL/F) of FTD or TPI following oral administration of TAS-102. Additional data provided (120D Response) indicated that of the patients from the pivotal study (RECOURSE trial) included in the population PK analysis, 96 had normal hepatic function, 42 had mild hepatic impairment, and no patients had moderate hepatic impairment. The daily AUC values for both FTD and TPI on Day 12 were comparable for patients with normal hepatic function and mild hepatic impairment (see below).

Table 18: RECOURSE trial (patients included in the population PK analysis); Summary of AUC for FTD and TPI for hepatic function groups

Hepatic Function	Parameter	FTD AUC (daily) Day 12	TPI AUC (daily) Day 12	BIL (mg/dL) baseline	AST (U/L) baseline
Normal TBIL ≤ ULN AST ≤ ULN)	n Mean ± SD (CV%)	96 45733 ± 12971 (28.4%)	96 724 ± 327 (45.2%)	96 0.50 ± 0.21 (41.3%)	96 23.4 ± 6.5 (27.9%)
Mild Impairment TBIL ≤ ULN; AST > ULN OR TBIL ≥ 1 to ≤ 1.5 x ULN, AST any	n Mean ± SD (CV%)	42 39404 ± 12408 (31.5%)	42 759 ± 501 (66.0%)	42 0.80 ± 0.37 (45.7%)	42 63.0 ± 30.2 (47.9%)
Moderate Impairment TBIL > 1.5x to ≤ 3x ULN, AST, any.	n Mean ± SD (CV)	0 NA	0 NA	0 NA	0 NA

AUC = Area under the curve (ng•hr/mL). BIL = Bilirubin. TBIL = Total bilirubin. FTD = trifluridine. TPI = Tipiracil.

The sponsor's 120D Response also included non-compartmental PK data (Day 1 and Day 12) relating to hepatic function for patients from two Phase I studies (TPU-TAS-102-102; TPU-TAS102-103). Inspection of the data showed that mild hepatic impairment had no significant effect on FTD or TPI exposure (AUC0-last) on Day 1 or Day 12. However, the number of patients with moderate hepatic impairment (n ≤ 2) was too small to draw meaningful conclusions about the PK of FTD and TPI in this group, and there were no data in patients with severe hepatic impairment.

Comment: The available data indicate that mild hepatic impairment does not increase systemic exposure (AUC) to FTD or TPI following administration of TAS-102. However, there were no data in patients with moderate or severe hepatic impairment. The sponsor indicated that a PK hepatic impairment study (Study TPU-TAS-102-106) will be completed by September 2017 and the CSR will be submitted to the EMA by the end of 2017.

4.9.2. Pharmacokinetics in subjects with impaired renal function

No dedicated clinical studies evaluating the effect of renal impairment on the PK of TAS-102 were submitted. In the population PK analysis, the mean ± SD CLCR of the patients included in the dataset (n = 238) was 103 ± 34 ml/minute (CV = 32.5%), with a median value of 103 mL/minute and a range of from 35 to 200 mL/minute. CLCR was a significant covariate for the CL/F of both FTD and TPI, with positive correlations being observed between CLCR and the CL/F of FTD and TPI. Urinary excretion was the main elimination route for TPI, but was a minor route of excretion for FTD. However, since TPI is a pharmacokinetic modulator that enhances the systemic exposure of FTD by inhibiting TPase, the CL/F of FTD would be influenced by TPI plasma concentration. Therefore, increased plasma concentrations of TPI in patients with renal impairment would be expected to increase systemic exposure to FTD. Based on the final model developed for CL/F of FTD, the mean relative ratio of AUC in patients with mild renal impairment (CLCR = 60 to 89 mL/min) and moderate renal impairment (CLCR = 30 to 59 mL/min) compared to patients with typical renal function (median CLCR = 103 mL/min) were estimated to be 1.08 to 1.32 and 1.33 to 1.87, respectively. The increment in AUC for FTD in patients with mild renal impairment was similar to the range of inter-individual variability for CL/F for FTD (CV = 32.2%), but was greater in patients with moderate renal impairment than inter-individual variability.

The sponsor's 120D Response included additional analyses based on renal function in patients from the pivotal study (RECOURSE trial) who contributed data to the population PK analysis. The

population PK analysis included 84 patients from RECOURSE with normal renal function, 38 patients with mild renal impairment and 16 patients with moderate renal impairment. Based on the patients from RECOURSE included in the population PK analysis, exposure (AUC) to FTD was 31% higher in patients with mild renal impairment compared to patients with normal renal function and 43% higher in patients with moderate renal impairment compared to patients with normal renal function, with the corresponding values for TPI being 34% and 65%, respectively. The results for patients from RECOURSE included in the population analysis are summarised below.

Table 19: RECOURSE trial (patients included in the population PK analysis); Summary of AUC for FTD and TPI for renal function groups

Renal Function	Parameter	FTD AUC (daily) Day 12	TPI AUC (daily) Day 12	CLCr Baseline
Normal	n	84	84	83
(CLcr ≥ 90 mL/minute	Mean ± SD (CV)	38812 ± 10905 (28%)	631 ± 301 (48%)	122 ± 20 (16.3%)
	GM Ratio (95% CI)	-	-	-
Mild Impairment	n	38	38	38
(CLcr 60-89 mL/minute)	Mean ± SD (CV)	50178 ± 11836 (34%)	826 ± 343 (42%)	75 ± 10 (13.5%)
	GM Ratio (95% CI)	1.31 (1.17, 1.46)	1.34 (1.13, 1.59)	-
Moderate Impairment	n	16	16	16
(CLcr 30-59 mL/minute)	Mean ± SD (CV)	54898 ± 13676 (25%)	1061 ± 617 (58%)	52 ± 4.6 (8.9%)
	GM Ratio (95% CI)	1.43 (1.22, 1.68)	1.65 (1.29, 2.11)	-

AUC = Area under the curve (ng•hr/mL). GM Ratio = ratio of AUC in normal group to the renal impairment group. CLCr = creatinine clearance mL/minute. FTD = trifluridine. TPI = Tipiracil.

The sponsor's 120D Response also included non-compartmental PK data (Day 1 and Day 12) for patients with renal impairment from 2 Phase I studies (Studies TPU-TAS-102-102; TPU-TAS102-103). Inspection of the data from this study showed that, in general, exposure (AUC0-last) to FTD and TPI on Day 1 and Day 12 increased in patients with mild renal impairment (n = 12 to 15), and moderate renal impairment (n = 5 to 7).

Comment: The available data indicate that systemic exposure (AUC) to both FTD and TPI increases in patients with mild and moderate renal impairment, with the increases being more marked in patients with moderate renal impairment. TPI is a PK modulator that increases the systemic exposure to FTD by inhibiting its metabolism by TPase. In TPU-TAS-102-104, the mean urinary excretion of FTD after a single 60 mg dose of TAS-102 was 1.5% of the administered dose (mean CL of FTD 2.9 mL/min), which suggests that urinary excretion plays a minor role in the clearance of TPI. Therefore, increased systemic exposure to FTD in patients with renal impairment is likely to be a secondary effect mediated by increased inhibition of TPase due to increased exposure to TPI resulting from renal impairment. There are no data in patients with severe renal impairment (CLCR = 15 to 29 mL/min) or End Stage Renal Disease (ESRD). The sponsor indicated that a PK renal impairment study (Study TPU-TAS-102-107) will be completed by September 2017 and the CSR will be submitted to the EMA by the end of 2017.

4.10. Pharmacokinetics according to age

In the population PK analysis (12DA25), the age of the patients in the dataset (n = 239) ranged from 33 to 82 years. The mean ± SD age of the total population was 60 ± 10 years, with a median of 61 years. Approximately 32% of the patient population were aged 65-74 years and 7% were aged 75-84 years, while there were no patients aged ≥ 85 years. Age was not a significant covariate for the PK parameters of Vd/F or CL/F for FTD or TPI. Therefore, the PK of FTD and TPI are not expected to be affected by age. The number of elderly patients aged ≥ 65 years in the TAS-102 PK studies is summarised below in Table 20.

Table 20: Number of elderly patients aged ≥ 65 years in the TAS-102 PK studies

PK Trials	Age: 65-74	Age: 75-84	Age: 85+
J001-10040010	3 /21 (14.3%)	0 /21 (0.0%)	0 /21 (0.0%)
J004-10040040	6 /16 (37.5%)	0 /16 (0.0%)	0 /16 (0.0%)
TPU-TAS-102-102 (Single-dose Contribution PK population, TAS-102)	8 /19 (42.1%)	0 /19 (0.0%)	0 /19 (0.0%)
TPU-TAS-102-102 (Multiple-dose PK population)	10 /38 (26.3%)	1 /38 (2.6%)	0 /38 (0.0%)
TPU-TAS-102-103 (PK population)	10 /44 (22.7%)	2 /44 (4.5%)	0 /44 (0.0%)
TPU-TAS-102-104 (all PK population)	15 /45 (33.3%)	3 /45 (6.7%)	0 /46 (0.0%)
TPU-TAS-102-301 (PK population who has estimated PK parameters)	45 /138 (32.6%)	11 /138 (8.0%)	0 /138 (0.0%)

4.10.1. Pharmacokinetics according to gender

In the population PK analysis (12DA25), the dataset (n = 329) included 41% female patients and 59% male patients. Initial modelling identified gender as a significant covariate for the Vd/F of FTD, but once BSA was incorporated into the model gender was no longer a significant covariate. Therefore, the apparent inter-individual difference on Vd/F of FTD seen for gender is attributable to the difference in body size, which is adjusted for by BSA dosing of TAS-102. Gender was not a significant covariate for any PK parameter of TPI.

4.10.2. Pharmacokinetics according to race

In the population PK analysis (12DA25), the dataset (n = 239) consisted of 61% Caucasian and 26% Asian (mainly Japanese) patients. Race was not a significant covariate for PK parameters of either FTD or TPI. Therefore, the PK of FTD and TPI are not expected to be affected by race. The potential racial difference in body size is adjusted for by BSA dosing of TAS-102.

4.11. Pharmacokinetic interactions

4.11.1. Pharmacokinetic interactions demonstrated in human studies

There were no dedicated PK drug-drug interaction clinical studies in humans. In the population PK analysis (12DA25), OCT2 inhibitors did not demonstrate significant effects on TPI, despite the product undergoing renal tubular secretion. Concomitant administration of OCT2 inhibitors had no effect on the PK parameters of FTD. However, these data should be interpreted cautiously as only 10% of the 239 patients in the dataset were receiving OCT2 inhibitors

4.12. Clinical implications of in vitro findings

4.12.1. Brief review of the submitted in vitro human biomaterial studies

The submission included a number of in vitro human biomaterial studies. Based on the reported results of these studies, clinically meaningful drug-drug interactions between the proposed fixed-dose tablet and other drugs appear to be unlikely. The reported results of the in vitro human biomaterial studies are summarised below.

4.12.1.1. Inhibition of CYP enzyme activity

Study XT115147 was undertaken to assess the inhibitory effects of FTD and TDI on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 in human liver microsomes. The concentrations of FTD and TPI in the reaction solution were set at 0.3 to 300 µmol/L and 0.1 to 100 µmol/L, respectively. The IC_{50} for CYP enzymes examined were reported at > 300 µmol/L for FTD and >100 µmol/L for TPI. The sponsor reported that there was little to no evidence of direct, time-dependent, or metabolism-dependent inhibition by FTD or TPI on any of the CYP enzymes examined. The sponsor concluded that, in vitro, FTD and TDI did not inhibit the CYP enzymes examined.

Study XT133055 was undertaken to assess the effects of FTY (0.1 to 100 µmol/L) on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5) in human liver microsomes in order to determine direct, time-dependent, or metabolism dependent inhibition. The sponsor reported that there was little to no evidence of direct, time-dependent, or metabolism-dependent inhibition of any of the CYP enzymes by FTY (all IC_{50} values were > 100 µmol/L). The sponsor concluded that, in vitro, FTY did not inhibit the CYP enzymes examined.

Comment: Neither FTD nor TPI are substrates of CYP. FTD, FTY, and TPI did not inhibit CYP enzymes in the in vitro human biomaterial studies.

4.12.1.2. Induction of CYP enzyme activity

Study XT133075 was undertaken to assess the potential of FTD, FTY, and TPI to induce CYP1A2, CYP2B6, and CYP3A4/5 in human cryopreserved hepatocytes using both CYP catalytic activities and CYP mRNA levels. Primary cultures of human hepatocytes from 3 donors were incubated for 72 hours with FTD (0.5, 5, and 50 µg/mL), FTY (0.1, 1, and 10 µg/ML), TPI (0.01, 0.1 and 1 µg/mL), and the positive control compounds omeprazole (50 µM for CYP1A2), phenobarbital (750 µmol/L for CYP2B6), rifampin (20 µmol/L for CYP3A4/5), or vehicle only. Fresh medium containing test compound was added every 24 hours. The sponsor reported that treatment of cultured human hepatocytes with FTY (up to 10 µg/mL), FTD (up to 50 µg/mL) or TPI (up to 1 µg/mL) for 72 hours caused less than a 20% increase in the percent lactate dehydrogenase released compared to the positive control. The sponsor concluded that FTD, FTY, and TPI are unlikely to induce CYP1A2, CYP2B6, and CYP3A4/5 in humans after oral administration.

Study 11DA19 was undertaken to assess the potential of FTD and TPI to induce CYP1A2 and CYP3A4 in human cryopreserved hepatocytes. Primary cultures of human hepatocytes from 3 donors were incubated for 72 hours with FTD (0.5, 5.0, and 50 µg/mL), TPI (0.01, 0.1 and 1 µg/mL), and the positive control compounds omeprazole (50 µmol/L for CYP1A2), rifampin (20 µmol/L for CYP3A4), or vehicle only. Fresh medium containing test compound was added every 24 hours. The catalytic activities of CYP1A2 and CYP3A4 were evaluated by phenacetin *O*-deethylase and midazolam 1'-hydroxylase, respectively. The sponsor reported that all positive controls induced appropriate increases in CYP activity. The effects of FTD and TPI on hepatocytes from 3 donors were reported not to have reached the 40% positive control threshold considered to indicate a positive inductive effect. The sponsor concluded that FTD and TPI are unlikely to induce CYP1A2 and CYP3A4 in humans.

Comment: The human biomaterial studies suggest that FTD, TPI and FTY are unlikely to induce CYP1A2, CYP2B6, and CYP3A4/5 in humans.

4.12.1.3. Displacement of protein binding

Protein binding of FTD in human serum was high, ranging from 96.7% to 97.3% (primarily to HSA) (Study AE-2350-3G). Study 12DA05 was undertaken to investigate the effect of FTD on the plasma protein binding of warfarin, a drug which also binds to albumin, and to examine the effect of FTD plasma protein binding on other drugs highly bound to HSA. The plasma protein binding ratio of warfarin was 99.0% in the absence of FTD, and 99.0%, 99.0% and 98.8% in the presence of 0.5, 5 and 50 μg/mL of FTD, respectively. The effect of plasma protein binding of FTD (5 μg/mL) in the presence or absence of other drugs highly bound to albumin was determined by ultrafiltration using ^{14}C-FTD. Warfarin, diazepam, and digitoxin bound to the three major drug binding sites of HSA. The HSA binding ratio of FTD was 93.1%, and 93.0%, 93.0%, 93.6%, 93.2%, 93.0%, and 93.9% when 1 μg/mL of warfarin, 10 μg/mL of warfarin, 0.2 μg/mL of diazepam, 2 μg/mL of diazepam, 0.1 μg/mL of digitoxin, and 1 μg/mL of digitoxin were added, respectively. Therefore, the extent of HSA binding of FTD was not affected by drugs that bind to albumin.

Comment: Drug interactions between FTD and other medicines that bind to HSA are unlikely.

4.12.1.4. Interactions mediated by human organic cation transporter 2 (OCT2)

Study 09B12 was undertaken to assess whether TPI is a substrate and/or inhibitor of human OCT2. The uptake of ^{14}C-TPI and the typical substrate of OCT2, ^{3}H-1-methyl-4-phenylpyridium (MPP+) were determined in cells stably expressing OCT2 and mock-transfected cells. The concentration-dependent uptake of ^{14}C-TPI at concentrations ranging from 0.000968 to 10 mmol/L indicated that TPI is a substrate for OCT2 in vitro. The IC_{50} for TPI as an inhibitor of OCT2 was 0.946 mmol/L (equivalent to 264 μg/mL), a concentration that was substantially higher than plasma Cmax values of TPI when TAS-102 was administered in clinical Study J001-10040010.

Comment: The sponsor concluded that TAS-102 is unlikely to cause significant interactions with other drugs due to inhibition of OCT2 by TPI, but the transport of TPI by OCT2 might be affected when TAS-102 is administered concomitantly with drugs that inhibit the OCT2 transporter. Consequently, the urinary excretion of TPI may be inhibited when co-administered with drugs that inhibit the OCT2 transporter resulting in increased plasma concentrations of TPI and FTD (secondary effect relating to TPI increase).

4.12.1.5. Interactions mediated by human organic anion transporters

Study 11CB14 was undertaken to assess whether TPI is a substrate and/or inhibitor of human OAT3. The uptake of ^{14}C-TPI or the typical substrate of OAT3, ^{3}H-estrone sulphate, was determined in cells transfected and stably expressing OAT3 and in mock-transfected cells. The uptake of ^{14}C-TPI into OAT3-expressing cells was reported to be higher than that observed in mock-transfected cells. The uptake ^{14}C-TPI was reported to be not time-dependent and markedly lower than that of ^{3}H-estrone sulphate, indicating that TPI is not a substrate of OAT3. The inhibitory effect of TPI (0.1 to 1 μmol/L) on the uptake of ^{3}H-estrone sulfate was also assessed, and showed that uptake was not inhibited by TPI at concentrations up to 1 μmol/L, a concentration higher than TPI plasma concentrations achieved when TAS-102 was administered in clinical studies.

Study 13DB16 was undertaken to determine the effects of FTD on human hepatic uptake transporters OATP1B1 and OATP1B3. The effects of FTD (0.5, 5, and 50 μg/mL) on the uptake of ^{3}H-estradiol-17β-glucuronide (E17βG) and ^{3}H-cholecystokinin-8 (CCK-8) into HEK293cells expressing OATP1B1 and OATP1B3, respectively, were evaluated. Cyclosporine A (positive control) was used as an inhibitor for both OATP1B1 and OATP1B3. The uptake of TPI by the human renal uptake transporter OAT1 was determined by the uptake of ^{14}C-TPI. The effects of TPI (0.01, 0.1, and 1 μg/mL) on the uptake of the typical OAT1 model substrate of TPI, ^{14}C-*p*-aminohippuric acid (PAH) were also determined, with probenecid being used as a positive control inhibitor for OAT1. The uptake of test compounds or typical probe substrates into cells was determined after incubation for up to 10 minutes at 37^{o}C.

The uptake of ^{14}C-FTD into OATP1B1- and OATP1B3-expressing cells compared to that in mock-transfected cells was reported to be similar to each other, indicating that FTD is not a substrate of

OATP1B1 or OATP1B3. The uptake of ^{14}C-TPI in OAT1 expressing cells compared with that of mock-transfected cells was reported to similar indicating that TPI is not a substrate of OAT1. The uptake of ^{3}H-E17βG into OATP1B1-expressing cells and the uptake of 3H-CCK-8 into OATB13-expressing cells were reported to be not inhibited by any concentration of FTD. Therefore, FTD is not an inhibitor of OATP1B1 or OATP1B3. The uptake of ^{14}C-PAH into OAT1-expressing cells was reported to be not inhibited by any concentration of TPI. Therefore, TPI is not an inhibitor of OAT1.

Comment: The in vitro data indicate that TPI is not a substrate or inhibitor of the OAT3 transporter and that FTD and TPI are not substrates or inhibitors of the OAT1 transporters.

4.12.1.6. Interaction mediated by human P-glycoprotein (P-gp)

Study 12DA17 was undertaken to assess the uptake of ^{14}C-FTD and ^{14}C-TPI using MDR1 membrane vesicles isolated from cultured Sf9 insect cells with forced expression of human P-gp. It was reported that although ATP-dependent uptake of *N*-methylquinidine (positive control) was observed in human MDR1 membrane vesicles, there was almost no uptake of ^{14}C-FTD and ^{14}C-TPI. The inhibitory effects of FTD (5 to 500 µmol/L) and TPI (2 to 200 µmol/L) on the uptake of N-methylquinidine were also examined. It was reported that the addition of the positive control verapamil (an inhibitor of P-gp) inhibited the uptake of *N*-methylquinidine by 99%, but FTD and TPI exhibited no inhibitory activity.

Comment: Neither FTD nor TPI is a substrate or inhibitor of MDR1. Therefore, drug interactions with TAS-102 mediated by human P-gp are unlikely.

4.12.1.7. Interaction mediated by BCRP

Study 13DB18 was undertaken to assess the membrane vesicular transport of FTD and TPI mediated by BCRP and to assess the inhibitory effect of FTD or TPI on the transport of the typical BCRP substrate methotrexate. The effects of FTD and TPI on the uptake of methotrexate into plasma membrane vesicles expressing BCRP were evaluated. Sulfasalazine, which is a typical inhibitor of BCRP, was used as a positive control. FTD (5, 50 and 500 µmol/L) and TPI (2, 20 and 200 µmol/L) were incubated with ^{3}H-methotrexate (0.271 µmol/L) in the presence of either 4 mmol/L magnesium-adenosine monophosphate (MgAMP) or 4 mmol/L magnesium-adenosine triphosphate (MgATP). It was reported that neither FTD (up to 500 µmol/L) nor TPI (up to 200 µmol/L) caused inhibition of BCRP-mediated uptake of ^{3}H-methotrexate. The amount of uptake of ^{14}C-FTD or ^{14}C-TPI into human BCRP-expressing vesicles and control vesicles was reported to be low in the presence of both adenosine monophosphate and adenosine triphosphate.

Comment: Neither FTD nor TPI is a substrate or inhibitor of BCRP.

4.12.2. Additional information relating to the in vitro human biomaterial studies

The CHMP provided a number of comments and questions relating to *the in vitro* human biomaterial studies and the sponsor provided 120D and 180D responses to the issues raised by the CHMP. The relevant additional information relating to the in vitro human biomaterial studies is briefly summarised below. However, it is recommended that the nonclinical evaluator review the additional data located in the submission.

The CHMP commented that it has been recently found that trifluridine (FTD) is taken up by cells mediated by nucleoside transporters. The sponsor provided data suggesting that the concentrative nucleoside transporter 1 (CTN1) and the equilibrative nucleoside transporter (ENT) may be involved in the absorption of FTD in the small intestine, and that CTN1, ENT1, and ENT2 may be involved in the tissue distribution of FTD.

The CHMP requested the sponsor to explore the potential relationship between thymidine exposure and trifluridine exposure following multiple dosing. Thymidine levels increased following TAS-102 treatment. High thymidine concentrations may compete with trifluridine for nucleoside transporters and thymidine kinase and affect the PK of trifluridine. The sponsor responded that, although endogenous thymidine levels increase after repeated administration of TAS-102, the

inhibitory effect of thymidine on the PK of trifluridine is unlikely since intrinsic thymidine level is negligible (approximately 100 ng/mL after repeated administration of TAS-102), and much lower than FTD or the inhibitory concentration of thymidine.

The CHMP requested the sponsor to 'provide convincing information to indicate whether inhibition of OCT2 is clinically relevant taking into account e.g. the relative contribution of secretion versus filtration to renal clearance, the known magnitude of effect of OCT2 inhibitors on sensitive substrates etc'. The sponsor provided data suggesting that, with a conservative assumption of a 75% inhibition of renal tubular secretion, the expected increase in exposure to TPI should be a 2 fold maximum. The sponsor also reported that data from the population PK model for patients who took TAS 35 mg/m^2 BD predicts that when TPI AUC0-τ increases 2 fold the corresponding increase in FTD is 28%, which is in the range of the inter-individual variability of FTD AUC (typically CV of 30%). Overall, the sponsor suggests that the data indicate that 'the inhibition of OCT2-mediated transport of TPI would not have a clinically significant effect on FTD exposure, and in turn the safety and efficacy of TAS-102'.

The CHMP stated 'that in most transport studies only 1 concentration of trifluridine and tipiracil was used to investigate if these compounds were a substrate for transporters. The concentration used was often higher than the Cmax observed in vivo. Therefore, it cannot be excluded that transport has been determined under conditions that the transporter was saturated. For that reason the transport studies investigating if trifluridine is a substrate for OATP1B1, OATP1B3, P-glycoprotein, BCRP and tipiracil for OAT1, OAT3, P-glycoprotein, and BCRP are considered inconclusive. The studies should be repeated over a range of substrates using clinically relevant concentrations'. The CHMP also requested the sponsor to 'investigate if tipiracil is a substrate and inhibitor of MATE (multidrug and toxin extrusion) transporters'.

The sponsor responded that it had investigated whether FTD and TPI are substrates of the transporters by comparing time-dependent uptakes of these compounds into transporter-expressing cells with those into vector-transfected (mock) cells, or by comparing time-dependent uptakes of these compounds into transporter-expressing vesicles in the presence or absence of cofactor (ATP). The sponsor conducted 'additional and preliminary' uptake studies for both FTD and TPI at lower substrate concentrations and reported that the results of the 'additional studies indicated that FTD is not a substrate for OATP1B1 or OATP1B3, and TPI is not a substrate for OAT1 or OAT3, which were consistent with (the original) results from studies conducted at the saturating substrate concentrations'. The sponsor provided additional data in its D180 Response to Outstanding Issues, and concluded that the functions of the transporter expressing cells were valid, and that FTD and TPI were not substrates for OAT1, OAT3, or OATP1B3.

The sponsor stated that uptake studies for FTD and TPI as substrates for efflux transporters (that is, MDR1 and BCRP) at lower concentrations than already studied were not feasible. Therefore, the sponsor reported that 'it can be reasonably concluded that FTD and TPI are not substrates for either MDR1 or BCRP, based on the results of uptake studies using transporter-expressing vesicles at the lowest feasible concentrations for FTD and TPI'.

The sponsor submitted a study for the membrane transport of TPI mediated by OCT1 and MATE (Study 12DB11). The study was reported to show that TPI was a substrate for OCT2 and MATE1 renal transporters, but was not a good substrate for OCT1, OCT3, or OCTN2. TPI was reported to inhibit tetraethylammonium (TEA) uptake mediated by OCT2 and MATE1 in a concentration-dependent manner, but the IC_{50} values for TEA uptake mediated by both transporters was stated to be much higher than blood concentrations of TPI at steady state after the recommended dose of TAS-102. The report concluded that 'TPI is secreted in urine by the renal transport systems for organic cation compounds, but does not inhibit their transport activities at clinical usage'.

The CHMP noted that *in vitro* studies showed that it is unlikely that FTD or TPI will affect the metabolism of a drug metabolised by any of the CYP enzymes tested or will interact with a drug that is metabolised by these enzymes. However, protein binding of FTY is not known. Therefore, the CHMP commented that the potential of FTY to inhibit CYP enzymes and the potential of FTY and

TPI to induce CYP enzymes cannot be predicted since the highest concentrations studied are lower than the maximum expected concentrations in the intestine, liver and kidney at clinical doses. The sponsor responded that the maximum concentrations of test drug to be used in the in vitro CYP inhibition studies were based on the ICH Guideline on the Investigation of Drug Interactions. The sponsor commented that the ICH guideline suggests that the same concentration should be used for the in vitro CYP induction and CYP inhibition studies. The sponsor provided data indicating that it had conducted the relevant in vitro studies at the appropriate concentrations of TPI and FTY. In the D180 Response to the List of Outstanding Issues, the sponsor indicated that the plasma protein binding ratio of ^{14}C-FTY was approximately 70%.

The CHMP noted that interactions for TPI with transporters OAT1 and OAT3 at clinically relevant concentrations cannot be predicted since the highest concentrations studied are lower than the maximum expected concentrations in the kidney at clinical doses. In response, the sponsor undertook additional studies investigating the inhibitory effects of TPI at concentrations up to 1 mM against OAT1- and OAT3-mediated transporters. The sponsor reported that the results of the additional investigations suggested that TPI had little potential to inhibit OAT1- and OAT3-mediated transporters even at 100 µmol/L, which was well over 50-fold of the mean unbound TPI Cmax (that is, 11.5 µmol/L). Therefore, the sponsor concluded that the in vitro inhibition studies support that TPI has no or little potential to inhibit OAT1- and OAT3-mediated transports in a clinically relevant situation.

In the D180 List of Outstanding Issues, the CHMP stated that according to the EMA guideline the potential induction effect by TPI on the intestinal, renal and hepatic CYPs cannot be fully ruled out due to the low concentration used in these studies. The sponsor responded that it will conduct an additional CYP induction study of TPI using the appropriate concentrations of TPI and will submit the study report to the EMA by the end of December, 2016.

4.13. Evaluator's overall conclusions on pharmacokinetics

The submitted data are considered to have adequately characterised the PK of trifluridine (FTD) and tipiracil (TPI) when administered as a fixed-dose combination tablet (TAS-102) at the proposed dose of 20 to 35 mg/m^2 BD (based on BSA) for the treatment of advanced mCRC. The PK data were based on studies in patients with advanced cancer (solid tumours). There were no PK data in healthy volunteers, but this is considered to be acceptable given that FTD is a cytotoxic agent. The PK results derived from non-compartmental analysis for the single-dose and multiple-dose studies contributing relevant PK data for FTD, TPI and relevant metabolites are summarised.

The major limitations of the PK data relate to the absence of dedicated clinical studies assessing the effects of hepatic and renal impairment on the PK of TAS-102. However, the sponsor has indicated that such studies will be submitted to the EMA by the end of 2017.

The submission included a number of human biomaterial studies investigating the in vitro effects of FTD and TPI on various enzyme systems relating to metabolism and potential drug-drug interactions. Data from these in vitro studies were presented in the submission. It is recommended that definitive evaluation of this in vitro data be undertaken by the nonclinical evaluator.

Two tablet formulations were used in the clinical studies (Early CTM and Late CTM formulations), and the TBM tablet formulation is stated by the sponsor to be identical to the Late CTM tablet formulation with the exception of ink imprinting. There were no clinical bioequivalence studies comparing the three formulations. However, in vitro dissolution data are reported to show similarity between the Early and Late CTM formulations. Based on the in vitro dissolution data the sponsor predicts that the in vivo performance of the Early and Late CTM formulations will be similar. In addition, the formulation similarities of the Late CTM and TBM formulations suggest that the in vivo performance of these two tablet formulations will also be similar. Overall, the in vitro data are considered to support the sponsor's decision not to submit dedicated clinical bioequivalence studies comparing the three tablet formulations. However, the definitive opinion about this matter rests with the pharmaceutical chemistry evaluator.

Based on the submitted data relating to solubility and permeability of FTD and TPI, the two products are reported to be BSC Class III compounds (that is, low permeability, high solubility). Following oral administration, both FTD and TPI are rapidly absorbed with mean Tmax values of 1 to 2 hours for FTD and 2 to 3.5 hours for TPI. No absolute bioavailability study was submitted. The sponsor provided a justification for not submitting an absolute bioavailability study. The justification has been examined and is considered to be satisfactory. Based on urinary and faecal radiolabelled excretion data from the mass balance study it can be estimated that following an oral dose of TAS-102 absorption of FTD is ≥ 57% to almost complete, and absorption of TPI is ≥ 27% to < 50% (TPU-TAS-102-108). Neither FTD nor TPI is a substrate or inhibitor of MDR1. Therefore, drug interactions with TAS-102 mediated by human P-gp are unlikely.

In place of an absolute bioavailability study, the sponsor submitted a single-dose relative bioavailability crossover study comparing tablets (20 mg x 3) to an oral solution (TPU-TAS-102-104). Based on the results for the AUC0-last, the relative bioavailability (tablet/solution) was 100% (95% CI: 93%, 109%) for FTD and 96% (90% CI: 86%, 107%) for TPI. The 90% CI for the geometric mean ratio of the Cmax for TPI (90% CI: 89%, 116%) was completely enclosed within the standard bioequivalence interval of 80% to 125%, but marginally outside the bioequivalence interval for the 90% CI for the geometric mean ratio of the Cmax for FTD (90% CI: 79%, 95%). Based on the overall results of the relative bioavailability study, the TAS-102 tablets used in the study (Late CTM; 20 mg) are considered to optimally formulated.

The effect of food on the PK of FTD and TPI was investigated in a single-dose (35 mg/m^2) crossover study in Japanese patients (Study J004-10040040). The geometric mean ratios (Fed/Fasting) for FTD were 96% (90% CI: 86%, 107%) for the AUC0-inf and 61% (90% CI: 50%, 73%) for the Cmax. The geometric mean ratios (Fed/Fasting) for TPI were 56% (90% CI: 48%, 64%) for the AUC0-inf and 58% (90% CI: 44%, 66%) for the Cmax. The study showed that, compared to the fasting state, food significantly reduced the AUC0-inf and Cmax values of TPI by 44% and 42%, respectively, and the Cmax value of FTD by 39%. The significantly lower Cmax values for FTD and TPI in the fed compared to the fasted state suggest that potential toxicities of TAS-102 might be reduced if the product is administered with food.

The effect of TPI on the bioavailability of FTD was investigated following a single-dose of TAS-102 containing FTD 35 mg/m^2 and TPI versus a single-dose of FTD 35 mg/m^2 alone (Study TPU-TAS-102-102). Based on the ratio of the geometric mean estimates (TAS-102/FTD), the FTD AUC0-last was approximately 37-fold higher following TAS-102 than FTD alone, and the FTD Cmax was approximately 22-fold higher following TAS-102 than FTD alone. The sponsor comments that simple extrapolation based on the AUC values indicates that the dose of FTD alone that would be necessary to achieve the FTD AUC observed after administration of TAS-102 is 1295 mg/m^2 (that is, 35 mg/m^2 x 37). The sponsor reported that this oral dose of FTD is predicted to exceed the projected lethal dose for humans of 1194 mg/m^2, based on primate toxicology studies. The equivalent dose in monkeys was reported to be associated with severe gastrointestinal and haematologic toxicities. The study supports the rationale for a fixed-dose combination product (FTD plus TPI) rather than FTD alone.

The AUC0-10h of FTD increased more than dose proportionally over the dose range 15 to 35 mg/^{2} BD, while the AUC0-10h of TPI increased dose proportionally over the same dose range (Study J001-10040010). Following multiple doses of TAS-102 (35 mg/m^2 BD), the AUC0-last of FTD accumulated approximately 3-fold on Day 12 compared to Day 1 and the Cmax accumulated approximately 2-fold (Study TPU-TAS-102-102). However, there was no further accumulation of FTD in subsequent cycles. There was no accumulation of TPI following multiple doses of TAS-102. The mechanism for accumulation of FTD following multiple daily dosing has not been identified.

Both the inter-subject and intra-subject variability in the PK of TAS-102 were investigated in Study TPU-TAS-102-104. The inter-subject variability of both FTD and TPI was high, with CV% values for AUC0-last and Cmax being 60.9% and 64.3%, respectively, for FTD and 54.3% and 58.6%, respectively, for TPI. The intra-subject variability of both FTD and TPI was moderate to low, with

CV% values for AUC0-last and Cmax being 16.4% and 25.4%, respectively for FTD, and 28.9% and 36.0%, respectively, for TPI.

In study TPU-TAS-102-102, the apparent volume of distribution was 21 L for FTD and 333 L for TPI following a single-dose of TAS-102 (35 mg/m^2). The population PK study estimated that the apparent volume of distribution (Vd/F) was 10 L (CV=25%) for FTD and 192 L (CV=63%) for TPI following multiple dosing with TAS-102 (Study 12DA25). In the PPK model, body surface area (BSA) was identified as a significant covariate of Vd/F for both FTD and TPI. No other tested covariates in the population PK model had a clinically meaningful effect on the Vd/F of FTD or TPI. Protein binding of FTD in vitro was greater than 96% and was independent of concentration, while protein binding of TPI did not exceed 8% in the presence or absence of FTD (Study AE-2350-25). FTD binds mainly to human serum albumin. Plasma protein binding of FTY (main metabolite of FTD) was approximately 70% (Study 15DB01). The human blood/plasma concentration ratios of both FTD and TPI were approximately 0.6, and were independent of concentration. The results for the human blood/plasma concentration ratios indicate that both FTD and TPI are distributed mainly to the plasma fraction.

In vitro human biomaterial studies showed that FTD and TPI are not metabolised by CYP enzymes. The in vitro studies demonstrated that FTD is metabolised primarily to FTY by thymidine phosphorylase (TPase), and that TPI is metabolised primarily to 6-hydroxymethyl uracil (6-HMU). The primary method of elimination of FTD is by metabolism to FTY in the intestinal tract and/or liver, while the primary method of elimination of TPI is by urinary excretion of unchanged TPI. In the mass balance study (Study TPU-TAS-102-108), the absorbed FTD was metabolised and then excreted in the urine as FTY and FTD glucuronide isomers. In the mass balance study (Study TPU-TAS-102-108), the absorbed TPI was excreted largely unchanged in the urine along with its major metabolite 6-HMU. The sponsor reports that the metabolites of FTD and TPI are pharmacologically inactive.

In study TPU-TAS-102-102, following single-dose and multiple-dose administration of TAS-102 (35 mg/m^2), the mean terminal half-lives on Day 1, Cycle 1 and Day 1, Cycle 12 were 1.4 and 2.1 hours, respectively, for FTD, and 2.1 and 2.4 hours, respectively, for TPI (Study TPU-TAS-102-102). In this study, the apparent oral clearance (CL/F) values were 10.5 L/h for FTD and 109.3 L/h for TPI. In the population PK study (Study 12DA25), the CL/F values were 2.93 L/h (CV=32.2%) for FTD and 88.7 L/h (CV=44.3%) for TPI. In the population PK analysis, baseline creatinine clearance (CLCR) was identified as a significant covariate for CL/F of both FTD and TPI, while baseline serum albumin (ALB) was identified as a significant covariate for CL/F of FTD (negative correlation possibly due to high protein binding of FTD).

In study TPU-TAS-102-104, urinary excretion was 1.5% for unchanged FTD, 19.2% for FTY (main metabolite of FTD), and negligible for other metabolites of FTD, while urinary excretion of unchanged TPI was 29.3%. The renal clearance (CLr) was 2.29 mL/min for FTD, 40.85 mL/min for FTY (main metabolite of FTD) and 292.67 mL/min for TPI. The CLr for TPI (approximately 293 mL/min) was approximately 3-fold greater than the CLcr for TPI (approximately 105 ml/min), indicating that TPI undergoes renal tubular secretion.

In the mass balance study (Study TPU-TAS-102-108), the total cumulative elimination of TRA derived from [14C]-FTD was approximately 60% of the administered dose. The majority of recovered TRA was eliminated into urine within 24 hours after oral administration (approximately 55%), and excretion into faeces and expired CO_2 was approximately 2.6% and 2.4%, respectively. Approximately 90% of plasma TRA was bound to plasma protein, and extractable TRA (6.67%) consisted of 52.7% FTD and 33.2% of FTY. The PK data showed that FTD and FTY accounted for approximately 12% of the total AUC of TRA in plasma. In urine, excreted TRA consisted of 45.9% FTY, 2.41% FTD, and 33.3% FTD glucuronide isomers. In faeces, multiple radioactive peaks were observed (trace levels). The major metabolite of FTD in the extractable fraction in plasma and urine was FTY. The overall recovery of radioactivity derived from [14C]-FTD administered with TAS-102 was relatively poor (approximately 60%) and is probably due to covalent binding to proteins.

In the mass balance study (TPU-TAS-102-108), recovered TRA of [14C]-TPI was approximately 77% of the administered dose, and consisted of approximately 27% urinary excretion and 50% faecal excretion. The overall recoveries were > 85% and reproducible for 3 of the 4 patients, whereas 1 patient exhibited extremely poor recovery at 36.3% of the dose. In plasma, extractable TRA consisted of 53.1% TPI and 30.9% 6-HMU, in urine, extractable TRA consisted of 79.1% TPI and 14.0% 6-HMU, and in feces, extractable TRA consisted of 48.2% TPI and 34.4% 6-HMU. It was noted that the 6-HMU metabolite appeared in plasma or in blood after disappearance of TPI, which according to the sponsor may suggest that 6-HMU was slowly produced via a metabolic pathway other than hepatic metabolism. Overall, TPI was the major moiety in plasma, urine, and faeces and 6-HMU was the major metabolite of TPI in these three matrices. No metabolites of TPI other that 6-HMU were detected at concentrations of greater than 5% in the plasma, urine or faeces. Based on TRA derived [14C]-TPI excreted into the feces and the urine, it can be estimated that the absorbed fraction of TPI was likely to be at least 27% but not greater than 50%. This suggests that the primary site of the inhibitory action of TPI on TPase might be in the intestinal tract rather than the liver.

The population PK study (Study 12DA25), indicated that age, gender and race were not significant covariates for either Vd/F or CL/F of both FTD or TPI. There was no dedicated clinical study investigating the effects of hepatic impairment on the PK of TAS-102. Data from RECOURSE suggests, the mild hepatic impairment is unlikely to significantly affect the PK of FTD or TPI. There were no data in patients with moderate or severe hepatic impairment. There was no dedicated clinical study investigating the effects of renal impairment on the PK of TAS-102. Data from RECOURSE suggests that both mild and moderate renal impairment can increase exposure. There were no data in patients with severe renal impairment or ESRD.

No dedicated clinical drug-drug interaction studies were conducted. In vitro studies with human biomaterials were reported to show that neither FTD nor TPI are metabolised by the broad range of CYP enzymes tested. In addition, FTD and FTY were reported not to inhibit or induce the CYP enzymes tested. It was also reported that the in vitro data showed that TPI did not inhibit or induce the CYP enzymes tested. However, in the CHMP expressed its concern that that the maximum concentration of TPI used in the CYP induction studies was too low to definitively exclude TPI mediated induction of CYP enzymes. The sponsor has indicated that it will conduct an additional CYP study investigation induction at higher TPI concentrations.

In vitro, FTD was reported not to be a substrate for MDR1, OATP1B1, OATP1B3 and BCRP, or to be an inhibitor of these transporters. In vitro, TPI was reported not to be a substrate for OAT1, OAT3, MDR1, and BCRP, or to be an inhibitor of these transporters. However, TPI in vitro was reported to be a substrate for, and an inhibitor of, the efflux transporters OCT2 and MATE1 at concentrations substantially higher than those anticipated in plasma in clinical practice. Therefore, TPI at recommended clinical doses is unlikely to cause drug-drug interactions due to inhibition of OCT2 and MATE1. However, as TPI is reported to be a substrate for OCT2 and MATE1 it is possible that urinary excretion of TPI might be reduced when TAS-102 is administered with inhibitors of these transporters. In vitro studies were reported to show that FTD is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The submission included the following studies with pharmacodynamic data:

- An exploratory PK/PD report of data collected during the pivotal Phase III study (the RECOURSE trial) relating to exposure–efficacy outcomes and exposure–safety outcomes.

- An analysis of cardiac safety, including the effect of TAS-102 on the QTc interval, was presented in Study TPU-TAS-102-103.
- An analysis of the correlation between haematologic toxicity and both the dosage and the pharmacokinetics of TAS-102 was presented in Study J001-10040010.

5.2. PK/PD analysis (RECOURSE)

The pivotal Phase III efficacy and safety study (RECOURSE) included an exploratory exposure-response analysis in patients in the TAS-102 treatment group who elected to participate in the optional PK assessment.

The study investigated the relationship between overall survival (OS), progression-free survival (PFS), and safety and exposure to FTD and TPI in the PK/PD population. Patients in the TAS-102 group who participated in the optional PK assessment were categorised into two sub-groups, based on median AUC values of FTD (43.51 h•ng/mL) and TPI (0.65 h•µg/mL), consisting of a high exposure group (> median AUC) and a low-exposure group (≤ median AUC).

Of the 800 randomised patients in the ITT analysis, 154 patients in the TAS-102 group and 80 patients in the placebo group consented to participate in the PK/PD study, and 139 (26.0%) patients in the TAS-102 group and 72 (27.1%) patients in the placebo group had samples collected at 1 or more post-dose time points on Day 12 of Cycle 1. One (1) of the 139 patients in the TAS-102 group was excluded from the PK/PD analysis due to missing actual sampling times for all blood collections. Therefore, a total of 138/534 (25.8%) patients in the TAS-102 group had evaluable PK parameters (that is, estimated AUC values for FTD and TPI) and were included in the PK/PD analysis. The analysis population is summarised below in Table 21.

Table 21: PK/PD Study; Study analysis population

	TAS-102 n (%)		Placebo n (%)
Signed Informed Consent in the Main Study	534		266
Signed Informed Consent PK Study	154		80
Populations			
Intent-to-Treat (ITT) [All Randomised]	534		266
As-Treated (AT) Population	533		265
PK/PD Population[a]	138 (25.8)		
Low FTD AUC (hr*µg/mL) ≤Median	69 (12.9)		
High FTD AUC (hr*µg/mL) >Median	69 (12.9)		
Low TPI AUC (hr*µg/mL) ≤Median	69 (12.9)		
High TPI AUC (hr*µg/mL) >Median	69 (12.9)		
Statistics for TAS-102 (FTD and TPI) AUC (hr*µg/mL)	**FTD**	**TPI**	
n	138	138	
Mean ± SD	43.81 ± 13.087	0.73 ± 0.387	
Median	43.51	0.65	
Min, Max	15.2, 84.6	0.2, 2.9	

a. Percentages based on number of patients randomised.

The baseline demographics and characteristics of the patient population are summarised. Patient demographics and baseline characteristics for most parameters were comparable for the 2 groups and within the patient subgroups defined according to median FTD or TPI AUC values. In the PK/PD population, 63% of all patients were male, 59% were White, 28% were Asian, 2% were Black, and data on race were not collected for 11% of patients. The median age of patients in the FTD high and low AUC groups was 65 years and 61 years, respectively, with 51% and 30% of patients, respectively, aged ≥ 65 years of age. The median age of patients in the TPI high and low AUC groups was 63 years and 61 years, respectively, with 46% and 35% of patients, respectively,

aged ≥ 65 years. There were about twice as many patients with mild to moderate renal impairment at baseline in the FTD and TPI high AUC groups compared to the FTD and TPI low AUC groups.

The median duration of exposure (weeks) was greater in the FTD high AUC group compared to the FTD low AUC group (13.86 versus 6.14 weeks), and lower in the TPI high AUC group compared to the TPI low group (6.71 versus 13.71 weeks). In the FTD group, the total number of cycles initiated and the median number of cycles per patient were higher in patients with high AUC values compared to patients with low AUC values (308 total cycles, median of 4.0 cycles versus 259 total cycles, median of 2.0 cycles). The corresponding mean ± SD number of cycles for the FTD high and low AUC groups were 4.5 ± 3.06 and 3.8 ± 2.91, respectively. In the TPI group, the total number of cycles initiated and the median number of cycles per patient were lower in patients with high AUC values compared to patients with low AUC values (292 total cycles, median of 2.0 cycles versus 275 total cycles, median of 4.0 cycles). The corresponding mean ± SD number of cycles for the TPI high and low AUC groups, were 4.2 ± 3.59 and 4.0 ± 2.27, respectively.

5.2.1. Results; Overall Survival (OS)

The OS relationships for the TAS-102 ITT population, the placebo population, and the TAS-102 PK/PD population are shown below in Table 22. Overall, in the TAS-102 PK/PD population the median OS was longer than the median OS in the both the TAS-102 ITT and placebo populations (8.9 versus 7.1 versus 5.3 months, respectively).

Table 22: PK/PD analysis; Overall survival in the TAS-102 ITT population versus the TAS-102 PK/PD population versus the placebo population

Parameter	TAS-102 (N = 533)	TAS-102 PK/PD Population (N = 138)	Placebo (N = 265)
Number (%) of patients by censoring			
Total	533 (100.0)	138 (100.0)	265 (100.0)
Not censored (dead)	363 (68.2)	81 (58.7)	209 (78.9)
Censored	170 (31.8)	57 (41.3)	56 (21.1)
Median Survival (months)[a] (95% CI)[b]	7.1 (6.5, 7.8)	8.9 (7.2, 10.2)	5.3 (4.6, 6.0)
Hazard Ratio (TAS-102:placebo) (95% CI)	0.68 (0.58, 0.81)	0.53 (0.41, 0.69)	

a. Kaplan-Meier estimates. b. Methodology of Brookmeyer and Crowley.

The results for OS by FTD AUC or by TPI AUC in the PK/PD population are summarised below in Table 23. Median OS in the high FTD AUC group was longer than in the low FTD AUC group (9.2 versus 8.1 months), but the HR was not statistically significant (HR (high:low)= 0.72 (95% CI: 0.46, 1.11)). The median OS in the high TPI AUC group was shorter than in the low TPI AUC group (7.8 versus 9.2 months), but the HR was not statistically significant (HR (high:low)= 1.09 (95% CI: 0.70, 1.69)).

Table 23: PK/PD Report; Overall survival by FTD AUC or TPI AUC in the PK/PD population

Parameter	High AUC (N = 69)	Low AUC (N = 69)
FTD		

Parameter	High AUC (N = 69)	Low AUC (N = 69)
Number (%) of patients by censoring status		
Total	69 (100.0)	69 (100.0)
Not censored (dead)	39 (56.5)	42 (60.9)
Censored	30 (43.5)	27 (39.1)
Median Survival (months)[a] (95% CI)[c]	9.2 (7.8, 11.1)	8.1 (5.3, 12.2)
Hazard Ratio (High AUC:Low AUC) (95%	0.72 (0.46, 1.11)	
TPI		
Number (%) of patients by censoring status		
Total	69 (100.0)	69 (100.0)
Not censored (dead)	42 (60.9)	39 (56.5)
Censored	27 (39.1)	30 (43.5)
Median Survival (months)[a] (95% CI)[b]	7.8 (6.1, 10.4)	9.2 (7.8, 12.2)
Hazard Ratio (High AUC:Low AUC) (95%	1.09 (0.70, 1.69)	

a. Kaplan-Meier estimates. b. Methodology of Brookmeyer and Crowley.

5.2.2. Results – Radiologic Progression-Free Survival (PFS)

Radiological PFS for the TAS-102 ITT, the TAS-102 PK/PD and the placebo populations are summarised below in Table 24. In the TAS-102 PK/PD population, the median PFS was longer than in both the TAS-102 and placebo populations (3.3 versus 2.0 versus 1.7 months, respectively).

Table 24: PK/PD Report; Radiologic Progression-Free Survival (PFS) in the TAS-102 ITT versus the TAS-102 PK/PD and versus the placebo populations.

Parameter	TAS-102 ITT Pop'n (N = 534)	TAS-102 PK/PD Pop'n (N = 138)	Placebo (N = 265)
Number (%) of patients by censoring status			
Total	534 (100.0)	138 (100.0)	265 (100.0)
Not censored (PFS event)	472 (88.4)	118 (85.5)	250 (94.3)
Progressed	432 (80.9)	113 (81.9)	226 (85.3)
Death	40 (7.5)	5 (3.6)	24 (9.1)
Censored	62 (11.6)	20 (14.5)	15 (5.7)
Median Progression-free survival (months)[a] (95% CI)[b]	2.0 (1.9, 2.1)	3.3 (1.9, 3.8)	1.7 (1.7, 1.8)
Hazard ratio (TAS-102:placebo) (95% CI)[b]	0.48 (0.41, 0.57)	0.36 (0.29, 0.46)	

a. Kaplan-Meier estimates. b. Methodology of Brookmeyer and Crowley.

The results for radiologic PFS by FTD AUC and by TPI AUC in the PK/PD population are summarised below in Table 25. Median radiologic PFS in the high FTD AUC group was longer than

in the low FTD group (3.7 versus 2.0 months), but the HR was not statistically significant (HR (high:low) = 0.82 (95% CI: 0.57, 1.18)). The median radiologic PFS in the high TPI AUC group was shorter than in the low TPI AUC group (2.0 versus 3.7 months), but the HR was not statistically significant (HR (high:low) = 0.97 (95% CI: 0.67, 1.41)).

Table 25: PK/PD Report; Radiologic progression free survival (PFS) by FTD AUC or TPI AUC in the PK/PD population

Parameter	High AUC (N = 69)	Low AUC (N = 69)
FTD		
Number (%) of patients by censoring status		
Total	69 (100.0)	69 (100.0)
Not censored (PFS event)	59 (85.5)	59 (85.5)
Progressed	58 (84.1)	55 (79.7)
Death	1 (1.4)	4 (5.8)
Censored	10 (14.5)	10 (14.5)
Median Survival (months)[a] (95% CI)[b]	3.7 (2.1, 3.9)	2.0 (1.9, 3.9)
Hazard ratio (High AUC:Low AUC (95% CI))	0.82 (0.57, 1.18)	
TPI		
Number (%) of patients by censoring status		
Total	69 (100.0)	69 (100.0)
Not censored (PFS event)	57 (82.6)	61 (88.4)
Progressed	55 (79.7)	58 (84.1)
Death	2 (2.9)	3 (4.3)
Censored	12 (17.4)	8 (11.6)
Median Survival (months)[a] (95% CI)[b]	2.0 (1.9, 3.7)	3.7 (2.1, 4.3)
Hazard ratio (High AUC:Low AUC (95% CI)	0.97 (0.67, 1.41)	

a. Kaplan-Meier estimates; b. Methodology of Brookmeyer and Crowley.

5.2.3. Results – Relationship between FTD/TPI exposure and safety endpoints

Grade ≥ 3 adverse events (AEs) for the FTD AUC and the TPI AUC in the PK/PD population are summarised below in Table 26. The incidence of both Grade ≥ 3 neutropaenia and any Grade ≥ 3 drug related AE was higher (> 10%) in the FTD high AUC group compared to the FTD low AUC group. Dose reductions (any) were higher in the FTD high AUC group (23%) than in the FTD low AUC group (9%). No specific pattern emerged between the TPI high AUC group and the low AUC group for safety events.

Table 26: PK/PD Report; Safety event summary by FTD AUC or TPI AUC, PK/PD population

Event	Number (%) of Patients			
	FTD		TPI	
	High AUC (>Median) (N=69)	Low AUC (≤Median) (N=69)	High AUC (>Median) (N=69)	Low AUC (≤Median) (N=69)
Grade 3 or Higher Neutropenia[a]	33 (47.8)	21 (30.4)	29 (42.0)	25 (36.2)
Relative Risk vs. Low AUC	1.57		1.16	
[95% CI]	[1.02, 2.42]		[0.76, 1.76]	
Grade 3 or Higher Thrombocytopenia[a]	3 (4.3)	2 (2.9)	3 (4.3)	2 (2.9)
Relative Risk vs. Low AUC	1.50		1.50	
[95% CI]	[0.26, 8.70]		[0.26, 8.70]	
Anaemia Grade 3 or Higher AE	15 (21.7)	12 (17.4)	14 (20.3)	13 (18.8)
Relative Risk vs. Low AUC	1.25		1.08	
[95% CI]	[0.63, 2.47]		[0.55, 2.12]	
Diarrhoea Grade 3 or Higher AE	3 (4.3)	4 (5.8)	2 (2.9)	5 (7.2)
Relative Risk vs. Low AUC	0.75		0.40	
[95% CI]	[0.17, 3.23]		[0.08, 1.99]	
Any Grade 3 or Higher AE	49 (71.0)	49 (71.0)	49 (71.0)	49 (71.0)
Relative Risk vs. Low AUC	1.00		1.00	
[95% CI]	[0.81, 1.24]		[0.81, 1.24]	
Any Grade 3 or Higher AE Related to Study Medication	39 (56.5)	31 (44.9)	36 (52.2)	34 (49.3)
Relative Risk vs. Low AUC	1.26		1.06	
[95% CI]	[0.90, 1.76]		[0.76, 1.47]	
Any Dose Reduction[b]	16 (23.2)	6 (8.7)	11 (15.9)	11 (15.9)
Relative Risk vs. Low AUC	2.67		1.00	
[95% CI]	[1.11, 6.41]		[0.46, 2.15]	

a. **Grade** 3 or higher based on laboratory data; b. Dose reductions based on exposure data. n = number of patients with an event.

The PK/PD report also included a descriptive analysis of the relationship between the neutrophil count (10^9/L) and both the FTD AUC and the TPI AUC during Cycle 1 by Week. The mean change in the neutrophil count (10^9/L) from Baseline at Cycle 1 at the Last Assessment was similar in the FTD low and high AUC groups (low: -2.225; high: -2.260) and in the TPI low and high AUC groups (low: -2.168; high: -2.316). The mean change in neutrophil count (10^9/L) from Baseline at the Cycle 1 Nadir was similar in the FTD low and high AUC groups (low: -3.105; high: -3.331) and lower in the TPI low compared to high AUC group (low: -2.952; high: -3.483).

5.3. Cardiac safety; Study TPU-TAS-102-103

5.3.1. Background

The submission included one Phase I study designed to evaluate the cardiac safety of TAS-102 in patients with advanced solid tumours (Study TPU-TAS-102-103). The study was undertaken in the USA (3 centres) and the UK (1 centre). The first patient was dosed on 30 May 2013, the last patient was dosed on 11 December 2013, and the cut-off date for the safety evaluation (completion of Cycle 1) was 9 January 2013. The final study report was dated 23 June 2014. The study was sponsored by Taiho Oncology, USA, and was conducted in accordance with ICH GCP Guidelines.

5.3.2. Objectives

The objectives of the cardiac safety evaluation (Cycle 1) were: (1) to investigate the effect of TAS-102 on cardiac repolarisation after single-dose and multiple-dose administration; (2) to evaluate the cardiac safety profile of TAS-102; and (3) to evaluate the relationship between the PK of TAS-102 and cardiac repolarisation (PK/PD analysis). The study also included an extension period (Cycles ≥ 2) in which the objectives were to assess the safety and the anti-tumour activity of TAS-102. Only the results of the cardiac safety evaluation will be discussed in this section of the CER.

5.3.3. Design

On the day prior to the start of TAS-102 dosing (Day -1, AM), all patients received a single-dose of placebo administered single-blind (patient-blinded). On Day 1 of Cycle 1, all patients received a single-dose of TAS-102 35 mg/m^2 in the morning and another single-dose of TAS-102 35 mg/m^2 administered 12 hours later (after collection of 12-hour PK sample). TAS-102 was then administered at a dose of 35 mg/m^2 BD on Days 2 through 5. This was followed by a recovery period from Day 6 through Day 7. TAS-102 35 mg/m^2 was again administered BD on Days 8 through 12. On Day 12 of Cycle 1, patients received the evening dose of TAS-102 after collection of the 12-hour PK sample. This was followed by a recovery period from Day 13 through Day 28. All doses of TAS-102 or placebo were administered within 1 hour after completing a meal. The dosing regimen in Cycle 1 was consistent with the dosing regimen proposed for registration for the proposed indication.

All patients had 12 hour Holter ECG recordings obtained within 48 hours prior to the first active TAS-102 dose (pre-dose baseline (Day -2)), after administration of placebo (single-blind (Day -1)), after administration of the first morning dose of TAS-102 on Day 1 of Cycle 1, and after the morning dose on Day 12 of Cycle 1. For each 12-hour recording, digital ECG data were extracted for analysis pre-dose (0) and then post-dose at 15, 30 min (minutes), 1, 2, 4, 6, 8, 10 and 12 hours (h).

Blood samples were collected for measurement of plasma concentrations of TAS-102 components (FTD and TPI) and the primary metabolite of FTD (FTY) after the morning doses of TAS-102 on Day 1 and Day 12 of Cycle 1. Blood samples were collected pre-dose (0) and then post-dose at 20 min, 35 min, 1 h 5 min, 2 h 5 min, 4 h 5 min, 6 h 5 min, 8 h 5 min, 10 h 5 min, and 12 h 5 min. The blood samples were taken 5 minutes after the digital ECG data extraction time points.

In addition to the Holter ECG recordings, standard 12-lead ECGs were obtained at screening (within 28 days prior to study drug administration), prior to administration of the morning dose of TAS-102 on Day 1 of Cycle 1, prior to administration of the morning dose of TAS-102 on Day 12 of Cycle 1, at the end of study treatment (or discontinuation of TAS-102), and at the 30 day Safety Follow-up Visit.

5.3.4. Patient population

The study population included patients over the age of 18 years with confirmed advanced solid tumours (excluding breast cancer) for which no standard therapy existed. There were 44 enrolled and treated patients. Four (4) patients discontinuations during the cardiac safety evaluation (Cycle 1), 2 for radiologic progression of the disease, 1 for clinical disease progression, and 1 for withdrawn consent. Of the 44 treated patients, 30 (68.2%) were evaluable for cardiac safety. The 14 (31.8%) treated patients not evaluable for cardiac safety included 9 with missing and/or inadequate ECG data, 3 who had taken prohibited medication, 2 for other reasons (low magnesium level 1 patient, low potassium level 1 patient), and 1 patient who was non-complaint with treatment.

Of the 30 patients evaluable for cardiac safety, the mean ± SD age was 58.9 ± 8.1 years (range: 41, 77 years), 50% were male and 50% were female, 86.7% were White, 6.7% were of Black/African heritage, and 6.7% were Asian. The ECOG PS was 0 in 70% of patients and 1 in 30% of patients. The majority of patients had colon cancer (76.7%), and 3.3% had rectal cancer.

5.3.5. Derivation of corrected QTc

For each scheduled time point for the cardiac safety evaluation, the average of the 3 ECG intervals from the triplicate were calculated and treated as a single observation. If fewer than 3 records were available, then the remaining records were averaged and used. Corrected QT intervals (QTc) were determined as follows:

- QT interval corrected for heart rate using a patient specific correction, QTcI: QTcI = QT/RRβi where βi is the patient-specific correction factor computed from a log linear model

log(QT) = αi + βi x log(RR) using information obtained at baseline (Day -2) from each individual patient i. The QTcI was considered the primary ECG parameter of interest.

- QT interval corrected for heart rate using Fridericia's correction, QTcF: QTcF = QT/ RR1/3.
- QT interval corrected for heart rate using Bazett's correction, QTcB: QTcB = QT/ RR1/2.

5.3.6. Derivation of derivation for ΔQTc and ΔΔQTc

For each patient, the corrected QT intervals collected at time t for baseline (Day -2), placebo (Day -1), single-dose and multiple-doses (Day 12) of TAS-102 were denoted as QTc(B)t, QTc(P)t, QTc(SD)t, QTc(MD)t, respectively, where time t = 0 hour, 15 min, 30 min, 1, 2, 4, 6, 8, 10, and 12 hours. The time-matched change from baseline (Day -2) to placebo (Day -1) or from baseline (Day -2) to TAS-102 dosing period (Day 1 and Day 12) in QTc interval at time t, denoted as ΔQTc, was defined as:

- ΔQTc(P)t = QTc(P)t - QTc(B)t
- ΔQTc(SD)t = QTc(SD)t - QTc(B)t
- ΔQTc(MD)t = QTc(MD)t - QTc(B)t

After calculation of ΔQTc, the placebo-adjusted baseline-subtracted QTc (ΔΔQTc) was determined. The ΔΔQTc was the time-matched difference between TAS-102 and placebo. ΔΔQTc was used as a response variable in a regression analysis over the plasma TAS-102 concentration.

- ΔΔQTc(SD)t = ΔQTc(SD)t - ΔQTc(P)t
- ΔΔQTc(MD)t = ΔQTc(MD)t - ΔQTc(P)t

For QT intervals with all corrections (QTcI, QTcF, and QTcB), ΔQTc and ΔΔQTc were calculated and summarised at each matching time point.

5.3.7. Primary endpoint analysis

The main objective of the QTc analysis was to determine whether TAS-102 had an effect on QT/QTc prolongation compared to placebo. The study specified that if the upper bound of the 1-sided 95% CI for the least-squares (LS) mean of the placebo-corrected, time-matched difference in QTc did not meet or exceed 20 ms at Day 1 and Day 12 of Cycle 1, it was to be concluded that TAS-102 had no clinically relevant QTc prolonging effect.

The primary endpoint in this study was the time-matched difference in the QTcI interval between TAS-102 and placebo. For each scheduled time point of ECG collection, the baseline-subtracted QTcI interval (ΔQTcI) was analysed using a repeated measure analysis of variance (ANOVA) for ECGs assessed during Day 1 (single dose) and Day 12 (multiple doses) of TAS-102 dosing to compare with placebo. The model included the factors of treatment (placebo, single-dose and multiple-doses of TAS-102), time, and treatment by time interaction. The measurements within each patient's treatment were treated as repeated measures. QTcF and QTcB intervals were analysed with the same ANOVA model used for QTcI to provide supportive data. The point estimate and the upper bound of the 1-sided 95% CI were provided between TAS-102 (single dose and multiple doses) and placebo for each time point. The point estimates and upper bound of the 1-sided 95% CI were plotted for QTcI, QTcF, and QTcB.

For the purpose of sample size determination, hypothesis testing was based on non-inferiority methods using the non-inferiority margin of 20 ms for the largest time matched QTcI difference between TAS-102 and placebo. Non-inferiority was to be concluded if the upper bound of the two-sided 90% CI (that is, upper bound of the 1-sided 95% CI) did not exceed 20 ms at any time point after dosing based on an Intersection-Union Test procedure. Based on the assumptions used to calculate the sample size, if the true difference in the QTcI between TAS-102 and placebo was ≤ 5 ms at all measurement time points, 30 evaluable patients would ensure at least 90% power.

Comment: In this study, it was pre-specified that TAS-102 would be considered not to have a clinically relevant effect on QT prolongation compared to placebo if the upper bound of the 1-sided 95% CI for the LS mean of the placebo-corrected, time-matched difference in QTc did not meet or exceed 20 ms at Day 1 and Day 12 of Cycle 1. This difference is greater than that specified in the TGA adopted EU guidelines relating to 'thorough QT/QTc studies' to evaluate QT/QTc interval prolongation for non-arrhythmic drugs (CHMP/ICH/2/204). In a TGA specific annotation to the guidelines it is stated that, 'QT prolongation would be of regulatory concern if either the estimated QT prolongation was > 5 ms or the upper bound of the 95% confidence interval was > 10 ms'. The sponsor stated that, because TAS-102 is a cytotoxic agent, it was not possible for ethical reasons to conduct a 'thorough QT/QTc study' in compliance with the guidelines.

In response to the 120D question raised by the CHMP about the use of the 20 ms non-inferiority margin, the sponsor stated that it 'is not uncommon in oncologic drug assessment to utilize a wider margin for the upper bound of the 95% CI based on risk versus benefit assessment (Sarapa, 2008)'. The sponsor noted that the upper bound of the 95% CI for ΔΔQTcI at 12-hours post-dose on Day 12 of the Cycle 1 was 10.3 ms, with the mean difference from placebo being 3.9 ms at that time point. In addition, all mean ΔΔQTcI values were within ± 5 ms. The sponsor concluded that, based on the primary analysis of the QTcI, 'TAS-102 is classified to the drugs that prolong the mean QT/QTc interval by around 5 ms or less and does not appear to cause Torsades de Pointe'.

5.3.8. Results

The results for the relevant QTcI LS mean placebo-adjusted change from baseline in 12-lead Holter Monitor (ms) for TAS-102 at Cycle 1, Day 1 and Cycle 1, Day 12 have been reviewed. At no time from 0.25 hours through to 12 hours post-dose on either of the two days did the upper bound of the 1-sided 95% CI for the difference between TAS-102 and placebo exceed 20 ms. Furthermore, the upper bound of the 1-sided 95% CI for the difference exceeded 10 ms at only one time-point (that is, 10.3 ms in Cycle 1, Day 12, at post-dose 12 hours). The mean difference between TAS-102 and placebo did not exceed 5 ms at any of post-dose time-points tested on either of the two evaluation days.

The results for the QTcF LS mean placebo-adjusted change from baseline in 12-lead Holter Monitor (ms) for TAS-102 at Cycle 1, Day 1 and Cycle 1, Day 12 have been reviewed. At no time from 0.25 hours through to 12 hours post-dose on either Day 1 or Day 12 of Cycle 1 did the upper bound of the 1-side 95% CI for difference between TAS-102 and placebo exceed 20 ms. However, the upper bound of the 1-sided 95% CI for the difference between TAS-102 and placebo exceeded 10 ms in Cycle 1, Day 1 at 12 hours post-dose (11.6 ms) and in Cycle 1, Day 1 at 12 hours post-dose (10.5 ms). The mean difference between TAS-102 and placebo exceeded 5 ms in Cycle 1, Day 1 at 12 hours post-dose (6.2 ms).

During placebo administration (Cycle 1 Day -1), there were 2 patients with a QTcI interval > 480 ms and ≤ 500 ms, and 4 patients with a QTcI interval > 450 ms and ≤ 480 ms. Following single-dose TAS-102 administration on Day 1, there was 1 patient with a QTcI interval > 480 ms and ≤ 500 ms, and 5 patients with a QTcI interval > 450 ms and ≤ 480 ms. Following multiple-dose TAS-102 administration on Day 12, there was 1 patient with a QTcI interval > 500 ms, 2 patients with a QTcI interval > 480 ms and ≤ 500 ms, and 4 patients with a QTcI interval > 450 ms and ≤ 480 ms. The results for the categorical increases in the QTcI interval are summarised.

No morphological changes were reported at any time point following placebo administration or single-dose or multiple-dose TAS-102 administration. Overall, no difference in ECG waveform results was reported with TAS-102 administration compared with placebo administration. All T waves and U waves were reported to be normal for all patients.

The relationship between the placebo-adjusted change from baseline in QTc interval versus plasma TAS-102 (FTD) concentration was assessed by a linear mixed effect model, with the individual QTc

change from time-matched placebo (ΔΔQTc) as the response variable and with treatment group and time-point as factors, corresponding log plasma concentration as a covariate, and patient as a random variable. From the linear mixed effect model results for QTcI, none of the upper bound of the 1-sided 95% prediction intervals exceeded the 20 ms non-inferiority margin for FTD, TPI or FTY plasma concentrations (Cmax). However, at the observed Cmax for FTD at 0.5 hours the upper bound of the 1-sided 95% CI exceeded 10 ms (that is, 11.7 msec).

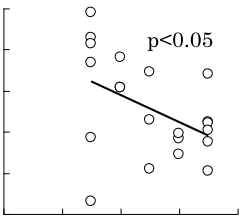
The results of the linear mixed effect model for the placebo-adjusted change from baseline in QTcF, QTcB, and uncorrected QT intervals were consistent with those for QTcI interval. None of the upper bound of the 1-sided 95% prediction intervals exceeded the 20 ms non-inferiority margin for the QTcF, QTcB, and uncorrected QT intervals.

No patient in the cardiac safety population (n = 30) experienced an AE of ventricular tachycardia, ventricular fibrillation, syncope, or seizure.

5.4. Relationship between haematologic toxicities and PK

In Study J100-10040010, the relationship between haematologic toxicity and both the dosage and PK of TAS-102 was examined in Japanese patients (n = 21). Linear regression analyses were conducted to evaluate the correlation between the percent decrease in white blood cell count, neutrophil count, platelet count and haemoglobin concentration and both the dosage and PK exposure parameters of TAS-102. There were significant correlations between percent decreases in the white blood cell count and the neutrophil count and dosage in all cycles tested, while no correlations were seen between dosage and percent changes in platelet counts and haemoglobin (see Figure 7, below).

Figure 7: Study J100-0040010; Correlation between the percent change in haematologic parameters in all courses and Tas-102 dosages



There were significant correlations between decreased white blood cell count and neutrophil count and the Cmax and AUC0-10h of FTD, FTY and TPI in Cycle 1 (Day 12), with similar results being found for all other cycles tested. There were significant correlations between decreased platelet count and the Cmax and AUC0-10h of TPI in Cycle 1 (Day 12) and all other cycles tested, while the AUC0-10h of FTD showed a significant correlation with decreased platelet in all cycles tested. There was a significant correlation between decrease in haemoglobin (%) and the AUC0-10h of TPI in

Cycle 1.

5.5. Evaluator's overall conclusions on pharmacodynamics

5.5.1. PK/PD efficacy analyses; OS and PFS

- In the PK/PD analysis (RECOURSE), median OS was longer in the FTD high AUC group than in the FTD low AUC group (9.2 versus 8.1 months), but the HR was not statistically significant (HR (high:low)= 0.72 (95% CI: 0.46, 1.11)). The median radiologic PFS in the FTD high AUC group was also **longer** than in the FTD low group (3.7 versus 2.0 months), but the HR was not statistically significant (HR (high:low) = 0.82 (95% CI: 0.57, 1.18)).
- In the PK/PD analysis (RECOUSE), the median OS in the TPI high AUC group was shorter than in the low TPI AUC group (7.8 versus 9.2 months), but the HR was not statistically significant (HR (high:low)= 1.09 (95% CI: 0.70, 1.69)). The median radiologic PFS in the TPI high AUC group was also shorter than in the TPI low AUC group (2.0 versus 3.7 months), but the HR was not statistically significant (HR (high:low) = 0.97 (95% CI: 0.67, 1.41)).
- Overall, in the PK/PD analysis (RECOURSE), OS and PFS appeared more favourable in the FTD high AUC group compared to the FTD low group, and in the TPI low AUC group compared to the TPI high AUC group. However, none of the pairwise comparisons were statistically significant, based on the 95% CIs for the HR analyses.

5.5.2. PK/PD safety analyses

- In RECOURSE, the incidence of both Grade ≥ 3 neutropaenia and any Grade ≥ 3 drug related AE was higher (> 10%) in the FTD high AUC group compared to the FTD low AUC group, and any dose reduction due to safety events was also higher in the FTD high compared to the low AUC group (23% versus 9%, respectively). However, no marked differences in Grade ≥ 3 neutropaenia, any Grade ≥ 3 drug related AEs or dose reduction due to safety events were observed between the TPI high and low AUC groups.
- In RECOURSE, mean changes in neutrophil count (10^9/L) from Baseline at Cycle 1 Last Assessment were similar in the FTD low and high AUC groups (-2.225 versus -2.260, respectively) and in the TPI low and high AUC groups (-2.168 versus -2.316, respectively). Mean changes in neutrophil count (10^9/L) from Baseline at the Cycle 1 Nadir were similar in the FTD low and high AUC groups (-3.105 versus -3.331, respectively), and marginally lower in the TPI low AUC group compared to the TPI high AUC group (-2.952 versus -3.483, respectively).
- In Study J100-10040010, there were significant correlations between percent decreases in both the white blood cell count and the neutrophil count and dosage in all cycles tested, while no correlations were seen between dosage and percent changes in platelet counts and haemoglobin. There were significant correlations between decreased white blood cell count and neutrophil count and the C_{max} and $AUC_{0\text{-}10h}$ of FTD, FTY and TPI in Cycle 1 (Day 12), with similar results being found in all other cycles tested. There were significant correlations between decreased platelet count and the C_{max} and $AUC_{0\text{-}10h}$ of TPI in Cycle 1 (Day 12) and all other cycles tested, while the $AUC_{0\text{-}10h}$ of FTD showed a significant correlation with decreased platelet in all cycles tested. There was a significant correlation between percent decrease in haemoglobin and the $AUC_{0\text{-}10h}$ of TPI in Cycle 1.

5.5.3. Cardiac safety – QTc prolongation and arrhythmogenic AEs

- The data from the Phase I study (TPU-TAS-102-103) undertaken in the USA and the UK showed that clinically significant effects of TAS-102 on QTc prolongation are unlikely to occur in patients treated with the medicine at the proposed dosed for the proposed indication. Overall, the cardiac safety data from Study TPU-TAS-102-103 showed that TAS-102 does not appear to

be arrhythmogenic, based on both the absence of clinically significant QTc prolongation and no reported AEs of ventricular tachycardia, ventricular fibrillation, syncope, or seizure.

6. Dosage selection for the pivotal studies

The sponsor states that between 1999 and 2006, 5 Phase I dose-finding studies (legacy studies) involving 111 enrolled and treated patients were conducted in the USA, with each study having a different TAS-102 dosing schedule and none of the studies having the TAS-102 dosing schedule proposed for registration (see Table 27, below). Based on reported preclinical findings (Study M96-029), the initial legacy studies employed daily dosing of TAS-102 in order to facilitate trifluridine (FTD) incorporation into tumour cells. In the first 3 legacy studies (Study TAS102-9801 (the first-in-human study), Study TAS102-9802, and Study TAS102-9803), the initial starting dose was 100 mg/m2 QD, which was reported to be 1/3 the toxic low dose in a 4-week toxicity study in monkeys. The results of these initial clinical studies indicated that TAS-102 was better tolerated when administered for 5 consecutive days rather than for 14 consecutive days, and the dose regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks was determined to be the optimal dose regimen.

The sponsor reported that, while these initial 3 studies were ongoing, results of nonclinical studies became available demonstrating significantly greater tumour reduction in mice following divided daily dosing compared with QD dosing (Study 11TA04). Therefore, 2 additional dose-finding studies were initiated to evaluate BD dosing (Study TAS102-9804) and TDS dosing (Study TAS102-9805), using the regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks. In Study TAS102-9804, which was conducted in heavily pre-treated breast cancer patients, the MTD was determined to be 50 mg/m^2/day, while in Study TAS102-9805, which was conducted in a patient population of primarily mCRC patients, the MTD was determined to be 70 mg/m2/day.

Table 27: Initial Phase I dose-finding studies conducted in the US, legacy studies

Study	N	Daily dose mg/m^2/day	Dosing frequency	Regimen	Prior therapies (median)	Malignancy % patients	MTD mg/m^2/day	DLT
TAS102-9801	14	50, 60, 100	QD	2 weeks with 1 week rest, repeated every 3 weeks.	4	CRC 100%	50	Granulo-cytopaenia
TAS102-9802	24	50, 70, 80, 110	QD	5 days with 2 days rest for 2 weeks, repeated every 4 weeks	2.5	CRC 83.3%	100	Granulo-cytopaenia
TAS102-9803	39	100, 110, 120, 130. 140, 150, 160, 170, 180.	QD	5 days every 3 weeks.	4	CRC 82.1%	160	Granulo-cytopaenia and others [a]
TAS102-9804	19	50, 60, 80	BD	5 days with 2	5	BC 100%	50	Granulo-cytopaenia

Study	N	Daily dose mg/m^2/day	Dosing frequency	Regimen	Prior therapies (median)	Malignancy % patients	MTD mg/m^2/day	DLT
				days rest for 2 weeks, repeated every 4 weeks				and others [b]
TAS102-9805	15	60, 70, 80	TDS	5 days with 2 days rest for 2 weeks, repeated every 4 weeks	3	CRC 100%	70	Granulo-cytopaenia and others [c]

QD = Once daily; BD=twice daily; TDS = three times daily; CRC = Colorectal cancer; BC = Breast cancer; MTD = maximum tolerated dose; DLT=dose limiting toxicity. a. Others: Grade 3 nausea, Grade 3 syncope, and Grade 3 dehydration; b. Others: Grade 3 diarrhoea, Grade 3 fatigue (2 patients), Grade 3 constipation, Grade 4 thrombocytopaenia; c. Others: Grade 3 fatigue.

Subsequent to the 5 initial US dose-finding studies, a study in Japanese patients (n = 21) with advanced solid tumours conducted in 2006 showed that TAS-102 was well tolerated in doses up to 70 mg/m^2/day (that is, 35 mg/m^2 BD) administered for 5 consecutive days rather than for 14 consecutive days, and the dose regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks (Study J001-10040010). In this study, significant correlations between FTD Cmax and the development of leukopaenia and neutropaenia were observed. Although the MTD was not established in Study J001-1004010, the recommended Phase II dose was determined to be 35 mg/m2 BD for 5 days a week with 2 days rest for 2 weeks, followed by a 14 day rest (1 treatment cycle) repeated every 4 weeks.

Subsequently, the recommended dose regimen identified in Japanese patients in Study J100-10040010 was confirmed to be tolerable in a study in a western (US) population (Study TPU-TAS-102-101). In this US Phase I, open label, non-randomised, dose finding tolerability study, patients (n = 27) with refractory mCRC who had received at least 2 prior lines of conventional chemotherapy for mCRC, (including a fluoropyrimidine, oxaliplatin, and irinotecan) no DLTs were observed in the 30 mg/m2 BD cohort (n = 3). Therefore, a total of 9 patients were enrolled in the higher dose 35 mg/m2 BD cohort, and 1 DLT was observed in this cohort (Grade 3 febrile neutropaenia). The DLT of febrile neutropaenia was considered to be related to the study drug. As only 1 of 9 patients in the 35 mg/m2 BD dose cohort experienced a DLT, this dose regimen was deemed to be tolerable and the MTD was established at 35 mg/m2 BD. Additional patients were enrolled in an expansion cohort at 35 mg/m2 BD. There were no complete or partial responses observed in the US study (Study TPU-TAS-102-101). However, in those patients who received the 35 mg/m2 BD dose, approximately 70% had a best overall response of stable disease.

The safety profile observed with TAS-102 in the Western (US) study (Study TPU-TAS-102-102) was consistent with that observed using the same TAS-102 dose regimen (35 mg/m2 BD) in a Phase II study in Japanese patients (n = 172) with mCRC (Study J003-10040030). In the FAS population in the Japanese Phase II study, median overall survival (OS) was 9.0 months in the TAS-102 group and 6.6 months in the placebo group (hazard ratio (HR)=0.56 (95% CI: 0.39, 0.81), p = 0.0011). Progression free survival (PFS) based on Independent Reader assessments was 2.0 months in the TAS-102 group and 1.0 month in the placebo group (HR=0.41 (95% CI: 0.28, 0.59), p < 0.0001). The disease control rate (DCR; partial response (PR) + stable disease (SD)) in the TAS-102 group was 43.8% compared to 10.5% in the placebo group (p < 0.0001). The most commonly reported side-effects in the Japanese Phase II study were bone marrow suppression and gastrointestinal-related

events. The toxicity profile seen in Japanese patients was qualitatively similar to that observed in the US Phase I study (Study TAS-102-101). The most frequent Grade 3 or 4 AE in both studies was neutropaenia. In the Japanese study, Grade 3 and 4 neutropaenia occurred in 31.9% and 18.6% of patients, respectively, and in the Western (US) study Grade 3 and 4 neutropaenia occurred in 40.9% and 13.6% of patients, respectively.

Based on the results obtained in the Japanese Phase II study in mCRC (Study J003-10040030), and the tolerability of the 35 mg/m2 BD regimen demonstrated in the US Phase I study in patients with CRC (Study TPU-TAS-102-101), a Phase III global study of TAS-102 (35 mg/m2 BD) in refractory mCRC colorectal cancer was initiated (TPU-TAS-102-103 = RECOURSE)

Comment: The dose regimen selected for the pivotal Phase III study (RECOURSE) was 35 mg/m^2 BD for 5 days a week with 2 days rest for 2 weeks, followed by a 14 day rest period (that is, 28 day cycle). The dose regimen is considered to be acceptable, based on the dose selection studies.

7. Clinical efficacy

7.1. Pivotal efficacy Study TPU-TAS-102-301 (RECOURSE)

7.1.1. Study design, objectives, locations and dates

7.1.1.1. Title

A randomised, double blind, Phase III study of TAS-102 plus best supportive care (BSC) versus Placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies. The study is also referred to as RECOURSE.

7.1.1.2. Locations and Dates

The patients in this study were randomised at a total of 101 study centres in 13 countries: United States (21), Japan (20), Spain (11), Italy (9), Germany (8), Belgium (6), France (6), Australia (5), United Kingdom (5), Austria (4), Ireland (3), Sweden (2), and Czech Republic (1). The first patient was randomised on 17 June 2012 and the last patient was randomised on 8 October 2013. The data cut-off dates were 24 January 2014 (overall survival data, observation of 571st death in the study) and 31 January 2014 (all clinical data except overall survival). The final report was dated 26 August 2014 and the revised report was dated 20 November 2014. The study was sponsored by Taiho Pharmaceutical Co., Ltd. (TPC) for sites in Region 1 (Asia (Japan)) and Taiho Oncology, Inc. (TOI) for sites in Region 2 (Western (Australia, Europe, US)). The clinical study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. The study was published in the New England Journal of Medicine, 14 May 2014.

7.1.1.3. Objectives

- The primary objective was to compare overall survival (OS) in the TAS-102 + best supportive care (BSC) arm (experimental arm) with the placebo + BSC arm (control arm).
- The key secondary objectives were comparison of progression free survival (PFS), and safety and tolerability in the two treatment arms.
- The other secondary objectives were time to treatment failure (TTF), overall response rate (ORR), disease control rate (DCR), duration of response (DR), and subgroup analysis by KRAS status on OS and PFS.
- The exploratory objectives included the effects of intrinsic and extrinsic factors on the PK of TAS-102, and the relationship between plasma concentrations of TAS-103 and safety and efficacy parameters.

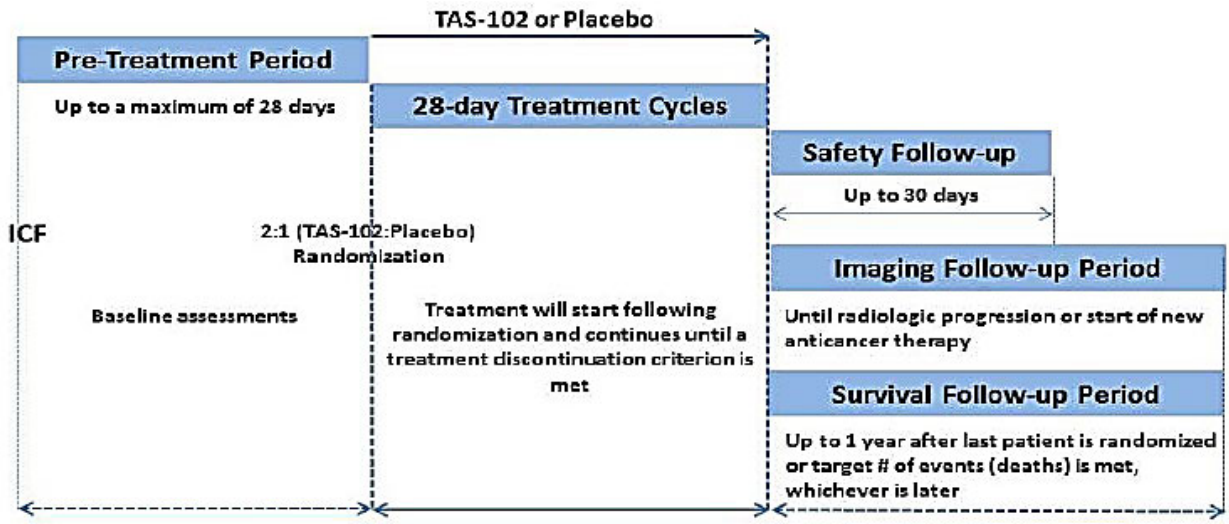
7.1.1.4. Design

RECOURSE was a Phase III, multinational, multicentre, randomised, double-blind, two-arm, parallel-group study designed to compare the efficacy and safety of TAS-102 plus BSC to placebo plus BSC in patients with chemotherapy-refractory metastatic colorectal cancer (mCRC). Patients (n = 800) were randomly assigned (2:1) to TAS-102 (experimental arm) or placebo (control arm).

Patients were to start study medication within 3 days after the date of randomisation and to continue treatment until a study treatment discontinuation criterion was met. The study medications were administered in 28 day cycles. Patients were evaluated for efficacy, including OS, PFS, TTF, ORR, DCR, and DR. Tumour assessments were performed throughout the study using contrast enhanced computed tomography (CT) scans based on Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1, 2009), with the best overall response as per the criteria being the best response from the start of study treatment until the end of treatment.

Safety monitoring began at the time the informed consent form (ICF) was signed and continued for 30 days after the last dose of study medication or until the initiation of another cancer therapy, whichever came first. Safety was assessed by AEs and laboratory evaluations. At selected sites, blood samples for PK analysis were collected from approximately 170 patients on Day 12 of Cycle 1 for exploratory analyses of population PK and exposure-response relationships. After the end of treatment, all patients were followed for survival at scheduled 8-week time intervals until death. Patients were to be followed for survival status until 12 months after the first dose of study medication for the last patient randomised. No patients were to be replaced at any time in the study. The study design is provided.

Figure 8: TAS-102; Study design



A patient was considered discontinued from study treatment when the decision to permanently stop study medication (TAS-102 or placebo) was made, including decisions made during study medication interruptions and recovery periods. Patients could be withdrawn from treatment for the following reasons:

- Patient request at any time irrespective of the reason;
- RECIST-defined disease progression;
- Clinical progression;
- Patient experienced an irreversible, treatment-related, Grade 4, clinically relevant, non-haematologic event;
- Unacceptable adverse events, or change in underlying condition such that the patient could no longer tolerate therapy, including, a maximum dose delay > 28 days from the schedule start of the next cycle, and need for more than 3 dose reductions of study mediation;

- Physician's decision; and
- Pregnancy.

A patient was considered 'Discontinued from Study Follow-up' only if one of the following occurred:

- Death;
- Survival follow-up period completed; or
- The study was completed or terminated by the sponsor or Regulatory Agencies. Patients who did not complete the study and for whom no survival data were available were considered to be lost to follow-up.

Comment: The sponsor stated that a placebo-controlled design was selected since, at the time the study was initiated, there were no standard therapies for patients with mCRC who had been previously treated with fluoropyrimidines, oxaliplatin, irinotecan, monoclonal anti-VEGF or anti-EGFR antibodies, and had become refractory or intolerant to those chemotherapies. Regorafenib was authorised for the treatment of patients with mCRC in all participating RECOURSE countries (Australia, EU, Japan and the US) only after enrollment was nearly complete (> 80%). Patients in both the TAS-102 and placebo treatment arms received BSC in addition to study medication. The sponsor stated that in order to ensure comparability of the treatment groups, patients were stratified by KRAS status (wild-type versus mutant), time since diagnosis of metastasis (<18 months versus ≥18 months), and geographic region (Region 1: Asia (Japan) versus Region 2: Western (Australia, Europe, US)). The study design is considered to satisfactory.

7.1.2. Inclusion and exclusion criteria

The study aimed to include approximately 800 adult and female patients with refractory mCRC. The inclusion criteria included male and female patients aged ≥ 18 years with definitive histologically or cytologically confirmed adenocarcinoma of the colon or rectum, with KRAS status determined (mutant or wild) and an Eastern Cooperative Group (ECOG) performance status (PS) of 0 or 1, who have received at least 2 prior regimens of standard chemotherapies for mCRC and are refractory to or failing those chemotherapies. Standard chemotherapies must have included all of the following agents approved in each country: fluoropyrimidines, irinotecan and oxaliplatin; an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab); and at least one of the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients. The exclusion criteria included a number of medical conditions, recent major surgery, recent radiotherapy, and recent anticancer treatments.

Comment: The inclusion and exclusion criteria are considered to be satisfactory. Treatments to which patients with mCRC must have been refractory include chemotherapies used in Australia for the condition. The inclusion criteria did not include patients who were refractory to regorafenib, since this medicine was not registered in any participating countries at the start of the study. In Australia, regorafenib is approved for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy; and patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

7.1.3. Study treatments

7.1.3.1. Study treatments

Each treatment cycle was 28 days in duration. The starting regimen was:

- Days 1 through 5: TAS-102 (35 mg/m^2/dose) or placebo orally BD times with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5.
- Days 6 through 7: Rest.
- Days 8 through 12: TAS-102 (35 mg/m^2/dose) or placebo orally BD times with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12.
- Days 13 through 28: Rest.

The study drugs were to be taken with a glass of water within 1 hour after the completion of morning and evening meals. The study drugs were administered based on BSA. If at the beginning of the next treatment cycle a patient's body weight decreases by ≥ 10% from Baseline, the dose was adjusted downwards based on the recalculated BSA. No increases in dose were permitted in cases where the body weight increased from Baseline.

7.1.3.2. Dose modifications; reductions and holds

Dose reductions were permitted in the case of toxicity. The protocol specified dose reductions were Level 1 from 35 mg/m^2 to 30 mg/m^2, Level 2 from 30 mg/m^2 to 25 mg/m^2, and Level 3 from 25 mg/m^2 to 20 mg/m^2. If dose modification failed to result in minimal criteria to resume treatment, study medication was discontinued. If the toxicities recurred after dose reduction to 20 mg/m^2, study medication was discontinued.

For all patients with decreased neutrophil and/or platelet counts, the next cycle of study treatment was not to be started until the resumption criteria were met. Patients who required more than a 28 day delay in the scheduled start of the next cycle were to have study medication discontinued. Uncomplicated neutropaenia or thrombocytopaenia ≤ Grade 3 did not require a dose reduction. Patients who experienced uncomplicated Grade 4 neutropaenia or thrombocytopaenia resulting in a > 1 week delay of the start of the next cycle were to start the next cycle at one reduced dose level. If the delay was ≤ 1 week, the patient was to start the next cycle at the same dose level.

If the patient recovered from the haematologic and non-haematologic toxicities and met the resumption criteria during the 2-week treatment period, and no dose reduction was required, study medication could be resumed during that cycle. If a dose reduction was required, the study drug was resumed at the start of the next cycle at the appropriate protocol specified dose level. If the study drug dose was reduced, it was not to be increased for subsequent cycles.

If the patient recovered from the haematologic and non-haematologic toxicities during the 2-week recovery period, the next cycle was to be started on schedule at the appropriate dose level specified in the protocol. If the toxicities did not recover during the treatment or rest period, the start of the next cycle could be delayed for a maximum of 28 days from the scheduled start date of the next cycle. If resumption criteria were met by this maximum 28 day delay, the next cycle could be started at the appropriate dose level specified in the protocol. Patients who required more than a 28 day delay in the scheduled start date of the next cycle had study medication discontinued.

7.1.3.3. Open label TAS 102

Subsequent to the database lock and completion of the primary analysis, there were 2 global amendments to the protocol that specified procedures to be followed for patients currently receiving placebo or who had previously received placebo to be offered treatment with open-label TAS-102. After completion of the primary analysis, if the primary endpoint of the study had been met and both efficacy and safety supported a favourable benefit/risk ratio for TAS-102, patients currently being treated with placebo and those previously treated with placebo were offered the option of open-label treatment with TAS-102.

7.1.3.4. Prohibited medications and therapies

Other than study medication, BSC, and permitted concomitant medications and therapies, patients were not permitted to receive any other medications and therapies, including other anticancer therapies. Palliative radiotherapy was not permitted while the patient was receiving study treatment.

7.1.3.5. Concomitant medication and therapies

If used concomitantly with TAS-102, antiviral drugs that are human thymidine kinase substrates (e.g., stavudine, zidovudine, telbivudine) were to be used with caution, because such drugs may theoretically compete with trifluridine for activation via thymidine kinases. The protocol recommended monitoring for decreased efficacy of such antiviral agents, with consideration being given to switching to alternative antiviral agents not known to be human thymidine kinase substrates (for example, lamivudine, zalcitabine, didanosine, abacavir).

Haematologic support could be administered as medically indicated (e.g., blood transfusions, granulocyte colony stimulating factor (G-CSF), erythropoietin) according to institutional standards. Standard procedures were also permitted for the management of diarrhoea, nausea and vomiting.

7.1.4. Efficacy variables and outcomes

7.1.4.1. Efficacy endpoints

Primary efficacy endpoint; Overall Survival (OS)

Overall survival (OS) was the primary endpoint. It was defined as the time (in months) from the date of randomisation to the date of death from any cause in the intention-to-treat (ITT) population. The primary analysis of OS included follow-up data (including death events) obtained through the date of the 571st death observed in the study. Patients having a documented survival status (alive or dead) after this date were censored at the cut-off date

Key secondary efficacy endpoint; Progression Free Survival (PFS)

Progression free survival (PFS) was defined as the time (in months) from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no radiological 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, or patients with clinical but not radiologic evidence of progression were censored at the date of the last radiologic evaluable tumour assessment before non-study cancer treatment was initiated.

Comment: In this study, progression was assessed by investigators rather than centralised assessors. This raises the possibility that the study was subject to bias due to potential subjective differences among investigators in the assessment of disease progression.

Other secondary efficacy endpoints

The time to treatment failure (TTF) was defined as the time (in months) from the date of randomisation until the date of radiologic disease progression, permanent discontinuation of study treatment, or death due to any cause. Patients who were still on study treatment at the cut-off date for the analysis were censored at the last date the patient was known to be on treatment. Censoring for TTF was also applied for those patients who were given non-study cancer treatment, with censoring at the time the patient began the non-study cancer treatment.

The overall response rate (ORR) was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR). The assessment of ORR was based on investigator assessment of radiologic images using RECIST criteria (version 1.1, 2009). The primary assessment of ORR was for the ITT population, and restricted to patients with measurable disease (at least 1 target lesion) at Baseline. 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 (excludes assessments during follow-up). If applicable, responses recorded after

radiologic disease progression or after initiation of non-study anti-tumour 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.

The disease control rate (DCR) was defined as the proportion of patients with best overall response of CR, PR, or SD.

The duration of response (DR), derived for patients with a best overall response of PR or CR, was defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause. Patients who were alive and progression free as of the analysis cut-off date were censored at their last evaluable tumour response assessment prior to initiation of any non-study cancer treatment.

7.1.5. Tumour assessment

Tumour assessments/imaging studies of the chest, abdomen, and pelvis (as clinically indicated) were obtained at each time point listed below for all patients:

- Baseline within 28 days prior to Day 1 Cycle 1.
- Every 8 weeks from the start of treatment.
- Within 2 weeks of the End of Treatment Visit if the patient had discontinued treatment for reasons other than radiologic disease progression. If an End of Treatment visit was not performed, tumour measurements were obtained at the time the patient was discontinued from treatment.
- For patients discontinuing treatment for reasons other than radiologic progression, every 8 weeks during the follow up period until the patient developed radiologic progression or the start of new anticancer treatment.

On site tumour assessments were made by the investigator according to the revised RECIST criteria (version 1.1, 2009). Results of these assessments, including response for target and non-target lesions and appearance of new lesions, were the basis for the continuation or discontinuation of study medication. The same method of assessment and the same technique was to be used to characterise each identified and reported lesion at Baseline, throughout the study and during follow up. The protocol specified that imaging-based evaluation was preferred to evaluation by clinical examination when both methods were used to assess the anti-tumour effect of treatment. Contrast enhanced CT was specified as the preferred method for tumour assessments. If contrast agent was contraindicated, then non-contrast chest CT and enhanced magnetic resonance imaging (MRI) of the abdomen (and pelvis if clinically indicated) was to be used. Images of the chest and abdomen (and pelvis if clinically indicated or obtained at Baseline) were required at each time point. Only CT and MRI were to be used for tumour measurement.

Clinical lesions were only considered measurable when they were superficial (for example, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, was recommended. Ultrasound was not to be used to measure tumour lesions that were clinically not easily accessible for objective response evaluation (e.g., visceral lesions). Ultrasound was a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Non-mandatory fluorodeoxyglucose positron emission tomography (FDG-PET) scans could be used to confirm diagnoses of suspicious lymph nodes. FDG-PET scan alone could not replace a MRI or contrast-enhanced CT.

On site assessments included the assessment of target and non-target tumour responses, and overall response. The assessments were made at the protocol specified time-points listed above. The response criteria for target and non-target lesions are summarised below.

Table 28: RECOURSE; Response criteria for target and non-target lesions

Target Lesions

Target Lesions	
Lesion Response	**Definition**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.
Non-Target Lesions	
Lesion Response	Definition
Complete Response (CR)	The disappearance of all non-target lesions. All lymph nodes must be non-pathological morphologically (that is, <10 mm in short axis in size).
Non-CR/Non-PD	A persistence of ≥1 non-target lesion(s)/ not reaching the extent of 'unequivocal progression.'
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (that is, substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy).

The overall response assessment criteria for patients with target (± non-target disease) and for patients with only non-target disease are summarised below.

Table 29: RECOURSE; Overall response criteria

Time point response for patients with target (± non-target) disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR (tumour marker must have normalised)
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-CR/Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Time-point response for patients with only non-target disease			
	Non-target Lesions	New Lesions	Overall Response
	CR	No	CR (tumour marker must have normalised)
	Non-CR/Non-PD	No	Non-CR/Non-PD
	Not all evaluated	No	Not evaluable
	Unequivocal PD	Yes or No	PD

Time point response for patients with target (± non-target) disease		
Any	Yes	PD

7.1.6. Randomisation and blinding methods

Patients were randomly assigned (2:1) to TAS-102 pus BSC (experimental arm) or placebo plus BSC (control arm) via a central Interactive Voice/Web Response System (IWRS) based on a dynamic allocation method (biased coin). Patients were stratified by KRAS status (wild versus mutant), time since diagnosis of first metastasis (< 18 months versus ≥ 18 months), and Region (Region 1: Asia (Japan) versus Region 2: Western (US and Europe)). Study medication was started within 3 days after the date of randomisation and continued until a study treatment discontinuation criterion was met.

This study is double-blind. TAS-102 tablets of each strength, 15 mg or 20 mg, and the corresponding placebo tablets, 15 mg placebo and 20 mg placebo, respectively, were identical in appearance and were packaged in identical containers. Until completion of the primary endpoint analysis, treatment assignment was blinded to all patients, investigators, ancillary study personnel at each study site, and to employees of the sponsor.

Unblinding of the study treatment was not to occur unless it needed to manage a patient's medical condition. If unblinding occurred the investigator was not disclose the unblinding information. After completion of the primary endpoint analysis, the treatment assignment for each patient was provided to the investigators.

Treatment assignment was unblinded and provided to the investigator for only 1 patient (placebo group) during the study for a SAE (ileus, not related to treatment) considered to be associated with disease progression (Cycle 1, Day 19). The patient was permanently discontinued from study treatment on Cycle 1, Day 21 (2 days prior to unblinding).

7.1.7. Analysis populations

- The intent-to-treat (ITT) population included all randomised patients and was the primary population for all efficacy analyses. All analyses using this population were based on the treatment assigned by IWRS.
- The tumour Response (TR) evaluable population included all patients in the ITT population with measurable disease (at least one target lesion) at baseline and with at least one tumour evaluation while on treatment. Patients with disease progression or with cancer related death prior to their first tumour evaluation were also to be considered evaluable. All analyses using this population were based on the treatment assigned by IWRS.
- The as-treated (AT) population included all patients who took part of any dose of the study treatment. This population was used for safety analyses. All analyses using this population were based on the treatment actually received.
- The pharmacokinetic (PK) population included patients at selected sites participating in the PK assessment who had evaluable plasma measurements with no significant protocol deviations that may impact the data.

7.1.8. Sample size

The study was designed to detect with 90% power a hazard ratio for OS of 0.75 (that is, 25% risk reduction) in the TAS-102 arm compared with the placebo arm, with a 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 3% per year loss to survival follow-up rate was assumed. Using a treatment allocation ratio of 2:1 (TAS-102: placebo) in 800 patients, a target of 571 events (deaths) was required for the primary analysis.

Based on these design characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target event milestone was projected to be reached approximately 5 months after the last patient was randomised. The median OS in the control arm

was estimated based on the observed median of 4.6 months in a similar control arm of the Phase III cetuximab study.[5] The estimated time-point was rounded to 5 months to reflect a higher control OS median in the Japanese population observed in the Phase II Study J003-10040030.

7.1.9. Statistical methods

7.1.9.1. Analysis of OS (primary efficacy endpoint)

The difference in OS between the two treatment arms was assessed in the ITT population using the stratified log-rank test from a Cox proportional hazards (CPH) model, including treatment and the 3 stratification factors in the model. The stratification factors were determined as per the IWRS assignment. Overall survival for each arm was summarised using Kaplan Meier curves, and was further characterised in terms of the median survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals (CIs) for the estimates. Confidence intervals for median overall survival were based on the methods of Brookmeyer and Crowley.[6] Assuming that OS demonstrates significance at the 1-sided 0.025 level, PFS could be subsequently tested at the 1-sided 0.025 level.

There were a number of supportive analyses of OS conducted in the ITT population (unless otherwise specified). These included:

- The unstratified log-rank test and a CPH model (that is, only treatment effect in the model);
- Multivariate analysis using the CPH model, including the 3 stratification factors and the following potential prognostic/predictive factors, age (< 65 versus ≥ 65), race (Caucasian versus Asian versus Other), gender, primary tumour site (colon versus rectal), ECOG PS (0 versus 1), number of prior regimens (2 versus 3 versus 4+), and number of metastatic sites (1 or 2 versus 3+);
- Subgroup analysis by KRAS status;
- Subgroup analyses for each of the other two stratification factors and the previously listed potential prognostic/predictive factors;
- The primary efficacy analysis excluding patients without documented refractory mCRC, as defined in the inclusion criteria;
- Additional sensitivity analyses as defined in the SAP;
- Stratified log-rank test using the final strata as recorded on the eCRF; and
- OS calculated using the date of the first dose of study medication in place of the date of randomisation.

7.1.9.2. Analysis of the key secondary efficacy endpoint (PFS)

The PFS was analysed for the ITT population using the methods described for OS. A sequential testing procedure was used. Assuming that OS demonstrated significance at the 1-sided 0.025 level, PFS could subsequently be tested at the 1-sided 0.025 level. In addition, several sensitivity analyses for PFS were conducted for the ITT population.

7.1.9.3. Other secondary efficacy endpoints

The statistical methods used to analyse the other secondary efficacy endpoints have been examined and are considered satisfactory. Standard methods were used to analyse time to event criteria and categorical criteria. All other secondary efficacy endpoints comparisons were made at the 2-sided 0.05 significance level. Time to event endpoints (PFS, TTF, DR) were analysed using the same survival methodology applied to the OS endpoint. The treatment comparison for both the ORR and BCR were based on the tumour response evaluable population using Fisher's exact test. Treatment estimates and differences were presented along with the associated 95% CIs.

Comment: Since PFS was the only key secondary endpoint for regulatory registration purposes, no statistical adjustments were made for the multiple pairwise comparisons used to test

the other secondary efficacy endpoints. Therefore, the other secondary efficacy endpoint analyses are considered to be exploratory rather than confirmatory.

7.1.9.4. Interim analyses

No interim analyses for efficacy or futility were planned or performed during this study. During the course of the study, an independent Data Monitoring Committee (DMC) periodically assessed the safety data.

7.1.9.5. Handling of dropouts or missing data

No missing data were estimated for efficacy variables except for imputation of dates for partial death dates or clinical progression dates in cases where only the day was missing. Dates with missing month or year were not imputed.

7.1.9.6. Changes to the planned analyses

There were no changes to the primary analyses of primary efficacy and key secondary efficacy endpoints as specified in the original protocol and version 1.0 of the SAP (dated 17 August 2012). However, subsequent to the final sign-off of version 1.1 of the SAP a number of relatively minor amendments were made to the SAP, which are considered not to have the affected the validity of the pre-specified statistical analyses of the efficacy endpoints.

7.1.10. Participant flow

A total of 1002 patients provided informed consent for participation in the study. Of these 1002 patients, 202 (20%) did not meet eligibility criteria and were not randomised (that is, screen failures). Of the 800 randomised patients (534, TAS-102; 266, placebo), 2 patients (1, TAS-102; 1, placebo) did not receive study medication. Of these 2 patients, 1 patient in the TAS-102 group discontinued prior to receiving treatment due to an AE of ascites and 1 patient in the placebo group was found to be ineligible for the study (entry criteria for serum bilirubin not met). All 798 as treated patients (533, TAS-102; 265, placebo) received their assigned treatment at randomisation, and 760 (95%) patients were evaluable for assessment of tumour response (TR Population). The disposition of the ITT population is summarised below.

Table 30: RECOURSE; Patient disposition, ITT population

	TAS-102 (n = 534)	Placebo (n = 266)
Not treated	1 (0.2%)	1 (0.4%)
As treated population	533 (99.8%)	265 (99.6%)
Patients still being treated as of 31 January 2014	37 (6.9%)	2 (0.8%)
Patients discontinued from study treatment	496 (92.9%)	263 (98.9%)
Adverse Event/SAE	19 (3.5%)	4 (1.5%)
>28 day delay	0	0
Patient had 3 dose reductions at time of DC	0	0
Both of the above	1 (0.2%)	0
Clinical Disease Progression	33 (6.2%)	31 (11.7%)
Radiologic Progression	416 (77.9%)	222 (83.8%)
Patient Withdrew Consent For Study Treatment	12 (2.2%)	1 (0.4%)
Death	7 (1.3%)	4 (1.5%)
Other	9 (1.7%)	1 (0.4%)
Patients discontinued from study follow-up	371 (69.5%)	214 (80.5%)
Death	367 (68.7%)	211 (79.3%)
Lost to follow up	3 (0.6%)	3 (1.2%)

	TAS-102 (n = 534)	Placebo (n = 266)
Patient refusal	1 (0.2%)	0

7.1.11. Major protocol violations

Predefined major protocol violations consisted of 2 types:

- Study entry criteria violations; and
- Study period violations.

Major protocol violations were reported in a similar proportion of patients in the TAS-102 and placebo arms (5.4% and 6.8%, respectively). Overall, only 33 of 800 (4.1%) patients in the ITT population had study entry criteria violations (19 (3.6%) TAS-102; 14 (5.3%) placebo). The most frequent entry criteria violation was inclusion of patients who were neither refractory nor intolerant to at least one of the required prior standard chemotherapies (3.0% (n = 16) TAS-102; 4.1% (n = 11) placebo).

Protocol violations reported during the study period occurred in a similar proportion of patients in the two treatment arms (1.9% (n = 10) TAS-102; 1.5% (n = 4) placebo), and all protocol violations in the study period consisted of prohibited concurrent cancer therapy administered while receiving study medication (that is, chemotherapy, surgery, radiotherapy). Eight patients (n = 8) in the TAS-102 arm and 2 patients in the placebo arm underwent surgery related to their cancer and 2 patients each in the TAS-102 and placebo arms had radiotherapy during the treatment period. No patients received other chemotherapy during the study treatment period.

7.1.11.1. Baseline data

The 2 treatment arms were comparable with respect to demographic and baseline characteristics. In the ITT population, the median age of the total population was 63 years, with 44% of the population being ≥ 65 years of age. Of the total patient population, 61% of patients were male, 58% were Caucasian/White and 35% were Asian/Oriental. All patients had a baseline ECOG performance status of 0 or 1. Fifty-one percent (51%) of patients had tumours categorised by investigators as KRAS mutant, and 49% of patients had KRAS wild-type at study entry. The time since diagnosis of metastasis was ≥ 18 months for the majority of patients (79%).

At the time of randomisation, patients were stratified based on KRAS status, time since diagnosis of metastasis, and geographical region. There were minor differences between IWRS assignment and final site assessments as recorded on the eCRF (after source data verification) for KRAS status and time since diagnosis of metastasis. In total, there were 22 patients (14, TAS-102; 8, placebo) with discordant stratification allocations for IWRS versus eCRF; 15 patients had discordant classifications for time since diagnosis of metastasis (10, TAS-102; 5, placebo) and 7 patients had discordant classifications for KRAS status (4, TAS-102; 3, placebo). The randomisation strata per IWRS and eCRF are summaries below.

Table 31: Randomisation strata per IWRS and eCRF, ITT population

Stratification Factor	Number (%) of Patients					
	Assignment per IWRS			Assignment per eCRF		
	TAS-102 (N = 534)	Placebo (N = 266)	Total (N = 800)	TAS-102 (N = 534)	Placebo (N = 266)	Total (N = 800)
KRAS gene type						
Wild-type	262 (49.1)	131 (49.2)	393 (49.1)	260 (48.7)	134 (50.4)	394 (49.3)
Mutant	272 (50.9)	135 (50.8)	407 (50.9)	274 (51.3)	132 (49.6)	406 (50.8)
Time since diagnosis of metastasis						
<18 months	111 (20.8)	55 (20.7)	166 (20.8)	107 (20.0)	54 (20.3)	161 (20.1)

Stratification Factor	Number (%) of Patients					
	Assignment per IWRS			Assignment per eCRF		
	TAS-102 (N = 534)	Placebo (N = 266)	Total (N = 800)	TAS-102 (N = 534)	Placebo (N = 266)	Total (N = 800)
≥18 months	423 (79.2)	211 (79.3)	634 (79.3)	427 (80.0)	212 (79.7)	639 (79.9)
Geographical region						
Asia (Japan)	178 (33.3)	88 (33.1)	266 (33.3)	178 (33.3)	88 (33.1)	266 (33.3)
Western (Australia, Europe, US)	356 (66.7)	178 (66.9)	534 (66.8)	356 (66.7)	178 (66.9)	534 (66.8)

The two treatment arms were well balanced with respect to KRAS status including KRAS mutation types as recorded on the eCRF. There was minimal discordance between KRAS as assigned via IWRS and as recorded on the eCRF, with KRAS wild-type gene being identified in 393 (49.1%) of the total population according to IWRS assignment and 394 (49.3%) of the total population on the eCRF. BRAF status was available for 15% (n = 124) of patients in the total ITT population, with the majority of these patients (n = 116) being wildtype. The KRAS and BRAF status based on the eCRF (ITT population) are summarised.

The two treatment arms were similar with respect to cancer diagnosis, including time from initial diagnosis and randomisation and time from confirmed metastasis to randomisation. The location of the primary tumour was colon in 63.3% (n = 338) of patients in the TAS-102 arm and in 60.5% (n = 161) of patients in the placebo arm, with the respective proportion of patients with primary rectal cancer being 36.7% (n = 196) and 39.5% (n = 161).

Table 32: Cancer diagnosis; ITT population

Parameter	TAS-102 (N = 534)	Placebo (N = 266)
Location of Primary Tumour, n (%)		
Colon	338 (63.3)	161 (60.5)
Rectal	196 (36.7)	105 (39.5)
Time from Initial Diagnosis to Randomisation (months)		
n	533	266
Mean (SD)	44.1 (29.32)	45.5 (28.28)
Median	36.0	39.0
Min, Max	8, 184	8, 170
Time from Confirmed Metastasis to Randomisation		
n	534	266
Mean (SD)	36.0 (22.16)	37.3 (21.83)
Median	31.0	32.0
Min, Max	5, 172	8, 154

The two treatment arms were comparable with respect to prior cancer therapies. Approximately 77% of all patients in the ITT population had undergone resection of the primary tumour, and approximately 26% had undergone prior radiotherapy. All patients had received prior systemic cancer therapy for treatment of metastatic disease. All patients had received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, and all but 1 patient had received bevacizumab. Eighteen percent (18%) of patients had also received regorafenib. All but 2 patients with KRAS wild-type tumours had received panitumumab or cetuximab. The majority of patients (61%) had received ≥ 4 prior systemic cancer therapies.

Of the 800 patients in the total ITT population, 60.6% (n = 485) had received a fluoropyrimidine containing regimen as their last regimen prior to randomisation (61.6% (n = 329) TAS-102; 58.6% (n = 156) placebo). The proportion of patients in the two treatment arms refractory to the last

prior regimen containing fluoropyrimidine was 94.5% (n = 311) in the TAS-102 arm and 92.3% (n = 144) in the placebo arm. The response to the last fluoropyrimidine regimen prior to randomisation is summarised.

The two treatment arms were similar with respect to the number and sites of target and non-target lesions at baseline. The mean (median) number of target lesions was 4.7 (2.04) in the TAS-102 arm and 4.9 (2.07) in the placebo arm. The most common target/non-target lesions were liver, lung and lymph nodes.

The proportion of patients with existing signs and symptoms by CTC grade was similar in the two treatment arms (76.9% (n = 410) TAS-102; 81.1% (n = 215) placebo). The most frequently reported conditions in both treatment arms were gastrointestinal disorders (36.2% (n = 193 TAS-102; 34.7% (n = 92) placebo), with individual events reported in ≥ 5% in both treatment groups (TAS-102 versus placebo) being constipation (12.8% versus 12.8%), abdominal pain (7.1% versus 9.1%), diarrhoea (7.1% versus 6.0%), and nausea (6.0% versus 6.8%). The proportion of patients with any prior medications was similar in the two treatment groups (89.9% (n = 479) TAS-102; 89.8% (n = 238) placebo).

7.1.12. Results for the primary efficacy outcome (OS)

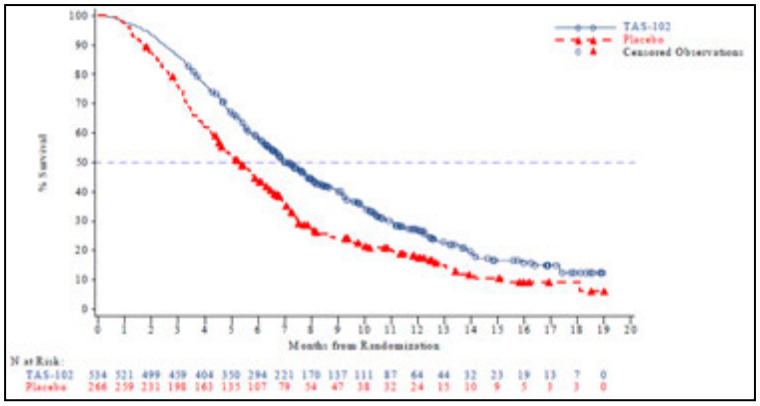
OS was defined as the time (in months) from the date of randomisation to the date of death for patients in the ITT population. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of 24 January 2014 (4 patients died on the calendar day of the pre-specified 571st event). The overall median follow-up for all patients was 11.8 months. The results for OS and the Kaplan-Meier curves are presented below.

Table 33: RECOURSE; Overall survival (OS), ITT population at the cut off date of 24 January 2014

Parameter	TAS-102 (N =)534)		Placebo (N = 266)	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (dead)	364 (68.2)		210 (78.9)	
Censored	170 (31.8)		56 (21.1)	
Survival (months) [a] (95% CI) [b]				
25th percentile	4.1	(3.8, 4.6)	3.1	(2.6, 3.4)
Median	7.1	(6.5, 7.8)	5.3	(4.6, 6.0)
75th percentile	12.3	(11.1, 13.8)	8.6	(7.5, 11.1)
Hazard ratio (95% CI)	0.68 (0.58, 0.81)			
P-value [c]	<0.0001 (1-sided and 2-sided)			
Percent (%) of patients surviving [a] (95% CI) [d]				
At 3 months	(86.0)	(82.7, 88.6)	(75.1)	(69.4, 79.9)
At 6 months	(57.8)	(53.5, 61.9)	(43.5)	(37.4, 49.4)
At 9 months	(40.1)	(35.6, 44.6)	(24.2)	(18.9, 29.9)
At 12 months	(26.6)	(22.2, 31.1)	(17.6)	(12.7, 23.1)

a) Kaplan-Meier estimates; b) Methodology of Brookmeyer and Crowley; c) Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region); d) Using log-log transformation methodology of Kalbfleisch and Prentice.

Figure 9: Overall survival (OS) Kaplan-Meier curves; ITT population at the cut off date of 24 January 2014



The sensitivity (supportive) OS analyses were consistent with the primary OS analysis, as were the OS analyses by stratification factors. There were a number of supportive subgroup analyses of OS, including analyses by stratification factors and geographical region, BRAF status, age, race, gender, primary tumour site, ECOG score, number of prior regimens, number of metastatic sites, prior regorafenib, and refractoriness to fluoropyrimidine in last prior regimen. The results for the OS analyses in the subgroups were consistent with the primary OS analysis in the ITT population, with survival favouring the TAS-102 arm compared to the placebo arm in all subgroup analyses apart from patients treated with 2 prior regimens.

Multivariate analyses of potential prognostic factors for OS in RECOURSE included KRAS status (wild versus mutant), time since diagnosis of first metastasis (< 18 months versus ≥ 18 months), region (Asia versus Western), BRAF status (wild, mutant, unknown), age (< 65 versus ≥ 65), race (Caucasian, Asian, Black/African American, not-collected), gender (male versus female), primary tumour site (colon, rectal), ECOG performance status (0 versus 1), number of prior regimens (2, 3, ≥ 4), and number of metastatic sites (1 or 2 versus 3). Following stepwise selection, the final Cox proportional hazards model included factors for treatment, KRAS status, time since diagnosis of first metastasis, region, primary tumour site, ECOG performance status, and number of metastatic sites. There were statistically significant interaction effects between treatment and the covariate factors included in the final model. In addition to treatment, three covariates were shown to have had a significant effect on OS (that is, time since diagnosis of first metastasis, ECOG performance status, and number of metastatic sites). The magnitude of the TAS-102 treatment effect after adjusting for all 3 significant prognostic factors was maintained, indicating that the prognostic factors do not add to the effect seen for treatment alone. The multivariate model estimate for the HR for TAS-102 relative to placebo remained at 0.69 ((95% CI: 0.58, 0.81); p < 0.0001), which is consistent with the primary analysis of OS in the ITT population.

In the D120 Response, the sponsor provided sensitivity analysis for OS excluding patients who had received prohibited anti-cancer treatments during the treatment period in violation of the protocol (10 (1.9%) TAS-102; 4 (1.5%) placebo). The HR for the OS analysis in these patients was 0.68 ((95% CI: 0.58, 0.81), p < 0.0001), which was identical to the primary analysis in the ITT population.

Comment: The primary efficacy endpoint analysis showed a statistically significant, but modest increase in median OS of 1.8 months in the TAS-102 arm compared to the placebo arm. The Kaplan-Meier curves began to separate in favour of TAS-102 at approximately 2 months after randomisation, and separation was maintained throughout the course of the study. The percentage of patients surviving at 1 year was estimated to be 26.6% in the TAS-102 arm and 17.6% in the placebo arm (Kaplan-Meier estimates). The treatment arms were similar with respect to non-study anti-tumour treatments received after discontinuation of study treatment and during follow-up. Therefore, it is reasonable to conclude that non-study anti-tumour treatment following treatment

discontinuation was not a confounding factor with respect to the OS results. The modest improvement in median OS in the TAS-102 arm should be interpreted in the context of treatment of patients with mCRC refractory to standard chemotherapeutic regimens. Overall, the sensitivity and subgroup analyses of OS were consistent with the primary OS analysis. In an ad hoc subgroup analysis based on geographical subgroups, median OS was numerically longer in the placebo arm compared to the TAS-102 arm in Australian patients (5.4 versus 3.8 months). However, the number of patients enrolled at Australian centres (n = 32 (n = 21, TAS-102; n = 11 placebo)) is too small to draw meaningful conclusion relating to survival differences between the two treatment arms.

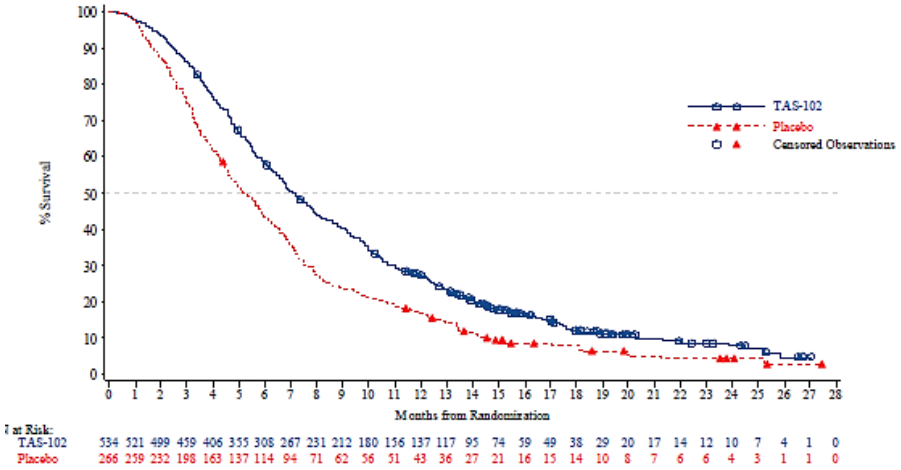
The data included an updated OS analysis based on a data cutoff date of 8 October 2014. This update was included in the sponsor's D180 response to the CHMP. The updated analysis included a total of 463 (86.7%) deaths in the TAS-102 arm and 249 (93.6%) deaths in the placebo arm. The median survival was 7.2 months (95% CI: 6.6, 7.8) in the TAS-102 arm and 5.2 months (95% CI: 4.6, 5.9) in the placebo arm, with a HR of 0.69 (95% CI: 0.59, 0.81), p < 0.0001 (1 sided and 2 sided), stratified log-rank test. The updated OS analysis was based on a total of 712 deaths in the ITT population compared to a total of 574 deaths in the ITT population in primary analysis. The OS results for the updated analysis were consistent with those for the primary OS analysis. The results for the updated OS analysis are summarised below, and the KM curves are presented below.

Table 34: Overall survival (OS); ITT population, updated data cut off 8 October 2014

Parameter	**TAS-102 (N = 534)**		**Placebo (N = 266)** [e]	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (dead)	463 (86.7%)		249 (93.6%)	
Censored	71 (15.3%)		17 (6.4%)	
Survival (months) [a] **(95% CI)** [b]				
25th percentile	4.1	(3.8, 4.6)	3.0	(2.6, 3.3)
Median	7.2	(6.6, 7.8)	5.2	(4.6, 5.9)
75th percentile	12.5	(11.2, 13.6)	8.4	(7.5, 10.7)
Hazard ratio (95% CI)	0.69 (0.59, 0.81)			
P-value [c]	< 0.0001 (1-sided and 2-sided)			
Percent (%) of patients surviving [a] **(95% CI)** [d]				
At 3 months	(86.0)	(82.7, 88.6)	(74.4)	(68.7, 79.2)
At 6 months	(58.0)	(53.7, 62.0)	(43.1)	(37.1, 49.0)
At 9 months	(40.2)	(36.0, 44.3)	(23.5)	(18.6, 28.7)
At 12 months	(27.1)	(23.3, 30.9)	(16.6)	(12.4, 21.4)

a. Kaplan-Meier estimates; b. Methodology of Brookmeyer and Crowley; c. Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region); d. Using log-log transformation methodology of Kalbfleisch and Prentice; e. Two patients randomised in the placebo group, initiated TAS-102 treatment (cross-over) after the study was unblinded in May 2014. For the ITT analysis presented in the above Table, both patients were still counted in the placebo group.

Figure 10: Overall survival (OS) Kaplan-Meier curves; ITT population, update cut off date 8 October 2014



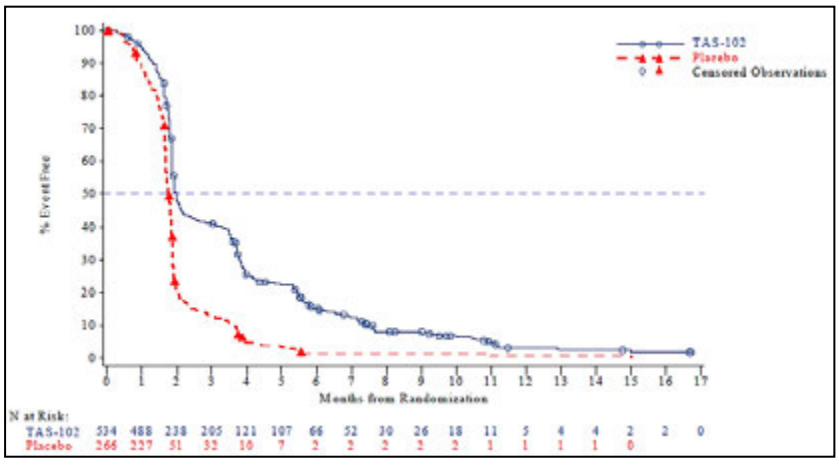
7.1.13. Results for the key secondary efficacy outcome (PFS)

PFS was defined as the time (in months) from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause as of the pre-specified cut-off date of 31 January 2014 for non-survival data. The results and Kaplan-Meier curves are summarised below.

Table 35: Radiologic progression free-survival (PFS); ITT population

	TAS-102 (n = 534)	Placebo (n = 266)
PFS event (total) – not censored	472 (88.4%)	251 (94.4%)
Progressed	432 (80.9%)	226 (85.0%)
Death	40 (7.5%)	25 (9.4%)
PFS (95% CI) – median (months)	2.0 (1.9, 2.1)	1.7 (1.7. 1.8)
Hazard Ratio (95% CI)	0.48 (0.41, 0.57)	
p-value, stratified log-rank test	p < 0.0001 (1-sided and 2-sided)	

Figure 11: Radiologic progression free survival (PFS); ITT population



Comment: There was a small statistically significant median increase in PFS of 0.3 months in the TAS-102 arm compared to the placebo arm. The majority of PFS events in both treatment arms were investigator-assessed radiological disease progression, with such events being reported more frequently in the placebo arm than in the TAS-102 arm (85.0% versus 80.9%, respectively). The Kaplan-Meier curves began to separate in favour of the TAS-102 arm from 2 months after randomisation. The results of the supportive analyses of PFS were consistent with the results of the primary analysis, as were the results based on the stratification factors. The median PFS results for the subgroup analyses numerically favoured the TAS-102 arm compared to the placebo arm for all subgroups, apart from the Australian subpopulation.

7.1.14. Other secondary efficacy endpoints

Time to treatment failure was defined as the time (in months) from the date of randomisation until the date of radiologic disease progression, permanent discontinuation of study treatment, or death due to any cause as of the pre-specified cut-off date of 31 January 2014 for non-survival data. The median TTF was 1.9 months for the TAS-102 arm compared to 1.7 months for the placebo arm with HR of 0.50 (95% CI: 0.42, 0.58), p < 0.0001 (stratified log-rank test).

The assessment of the overall response rate (ORR) was based on investigator review of radiologic images and was restricted to patients with measurable disease (at least 1 target lesion) at baseline and with at least one tumour evaluation while on study treatment (TR population). There was no statistically significant difference between the two treatment groups in the ORR. There was a statistically significant difference between the two treatment groups in favour of TAS-102 compared to placebo in the disease control rate (DCR). Of note, only 1 patient (placebo group) achieved a complete response. The results are summarised below.

Table 36: Best overall response rate (ORR) and disease control rate (DCR), TR population

Parameter	**TAS-102 (N = 502)**		**Placebo (N = 258)**	
Best overall response (ORR)	**n (%)**	**95% CI [a]**	**n (%)**	**95% CI [a]**
Complete or partial	8 (1.6)	0.7, 3.1	1 (0.4)	0.0, 2.1
Complete	0 (0.0)		1 (0.4)	
Partial	8 (1.6)		0 (0.0)	
Stable disease	213 (42.4)		41 (15.9)	
Progressive disease - radiological	260 (51.8)		195 (75.6)	
Not evaluable [b]	21 (4.2)		21 (8.1)	
Complete, partial or stable disease (DCR)	221 (44.0)	39.6, 48.5	42 (16.3)	12.0, 21.4
Difference in ORR (TAS-102 – placebo) (95% CI)	1.2 (-0.1, 2.5)			
P-value [d]	0.2862			
Difference in DCR (TAS-102 – placebo) (95% CI)	27.7 (21.5, 34.0)			
P-value [d]	<0.0001			

a. Exact 2-sided confidence interval based on Clopper-Pearson methodology; b. Patients with a cancer-related death but no tumour evaluation while on study treatment; c. Normal approximation; d. Fisher's Exact test (2 sided).

In the pre-specified analysis of time to worsening ECOG PS status ≥ 2 in the ITT population, the median time to ECOG PS ≥ 2 was 5.7 months in the TAS-102 arm compared to 4.0 months in the placebo arm with HR of 0.66 (95% CI: 0.56, 0.78), p<0.0001 (stratified log-rank test). Inspection of the Kaplan-Meier curves for time to ECOG performance status ≥ 2 showed that the curves began to separate in favour of the TAS-102 arm at about 2 months and remained separated throughout the remainder of the study.

7.1.15. Efficacy in special populations

7.1.15.1. Age

In the subgroup analyses based on age, median OS was longer in the TAS-102 group than in the placebo group for patients aged < 65 years (7. 1 versus 5.7 months; HR = 0.74 (95% CI: 0.59, 0.94)), and for patients aged ≥ 65 years (7.0 versus 4.6 months; HR = 0.62 (95% CI: 0.48, 0.80)). There were no data for patients aged ≥ 85 years. The data (D120 Response) included the results for OS and PFS based on age.

Table 37: RECOURSE; OS by age subgroup, ITT population

Age	TAS-102 n = 534		Placebo n = 266		TAS versus PBO n = 800
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
<65	300	7.1 (6.5, 8.4)	148	5.7 (4.9, 6.5)	0.74 (0.59, 0.94)
65 to 74	198	7.2 (6.3, 8.1)	94	4.5 (3.9, 5.9)	0.58 (0.43, 0.77)
75 to 84	36	6.5 (4.8, 9.1)	24	6.6 (2.9, 7.5)	0.89 (0.45, 1.74)

Table 38: RECOURSE; PFS by age subgroup, ITT population

Age	TAS-102		Placebo		TAS versus PBO
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
<65	300	1.9 (1.9, 2.0)	148	1.7 (1.7, 1.8)	0.52 (0.42, 0.65)
65 -74	198	2.1 (1.9, 3.5)	94	1.7 (1.7, 1.8)	0.36 (0.27, 0.47)
75 – 84	36	2.0 (1.7, 3.9)	24	1.9 (1.8, 1.9)	0.66 (0.33, 1.32)

7.1.15.2. Gender

In the subgroup analyses based on gender, median OS was longer in the TAS-102 arm than in the placebo arm for both male patients (7.3 versus 5.0 months; HR = 0.69 (95% CI: 0.56, 0.87)), and female patients (6.8 versus 5.6 months; HR = 0.68 (95% CI: 0.51, 0.90)).

7.1.15.3. Race

In the subgroup analyses based on race, median OS was longer in the TAS-102 arm than in the placebo arm for Caucasian/White patients (6.3 versus 4.9 months; HR = 0.66 (95% CI: 0.52, 0.83)), and Asian/Oriental patients (7.8 versus 6.3 months; HR = 0.75 (0.57, 0.98)). There were too few Black patients to make a meaningful comparison on OS between the two treatment groups.

7.2. Study J003-10040030 – Supportive study

7.2.1. Study design, objectives, locations and dates

7.2.1.1. Title

A placebo controlled, multicentre, double blind, randomised, Phase II Study of TAS-I02 in patients with unresectable advanced or recurrent colorectal cancer who have had 2 or more chemotherapy regimens and who are refractory or intolerant to fluoropyrimidine, lrinotecan, and oxaliplatin.

7.2.1.2. Locations and Dates

The CSR for this study was provided as a translation from Japanese. The study was undertaken at 19 sites in Japan. The first patient was enrolled on 25 August 2009 and the data cut off date for the final CSR was 13 April 2011. The final study report was signed on 31 August 2011. The study was sponsored by Taiho Pharmaceutical Co., Ltd., Tokyo, Japan. The study was stated to have been conducted in compliance with the 'standards related to the implementation of clinical drug trials

(Good Clinical Practice (GCP)' on the basis of the Declaration of Helsinki. The study was undertaken prior to RECOURSE, and appears to have formed the basis for approval of TAS-102 in Japan.

7.2.1.3. Objectives

The primary objective was to evaluate and compare overall survival (OS) following treatment with TAS-102 or placebo in patients with unresectable advanced or recurrent colorectal cancer who have had 2 or more chemotherapy regimens and who are refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin.

The secondary objectives were to evaluate and compare the TAS-102 group and the placebo group with respect to the following: response rate (RR); duration of response (DR); disease control rate (DCR); progression free survival (PFS); time to treatment failure (TTF); adverse event profile and tolerability; and measurement for codon 12 and 13 mutations of the KRAS gene in tumour tissue and effect of TAS-102 with respect to the existence of a KRAS mutation.

The exploratory objectives were to assess the effect of FTD on DNA using the comet assay method, and to assess the correlation between the volume of TK1 and TP protein tumour tissue and clinical effects.

7.2.1.4. Design

The study was a double blind, placebo controlled comparative, Phase II study undertaken in multiple centres in Japan. The study was designed to evaluate the efficacy and safety of TAS-102 administered at a dose of 70 mg/m^2 per day in patients with unresectable advanced/recurrent colorectal cancer patients who had received 2 or more chemotherapy regimens and were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin. Patients who met the eligibility criteria were randomised (2:1) to TAS-102 or placebo, with randomisation being stratified by ECOG performance status (PS = 0 versus PS = 1/2).

Tumour assessments were performed every 4 weeks for the first 12 weeks of study treatment and thereafter every 8 weeks during study treatment. Tumour response was assessed by an independent review committee according to RECIST criteria (version 1.0), as well as by investigators. The protocol stated that the independent assessment of the anti-tumour effect using RECIST criteria for radiological imaging were to be used for the primary analysis. After the end of treatment, patients were followed for survival at scheduled 12-week intervals.

Treatment with the investigational drugs was initiated within 8 days of randomisation and continued until specified discontinuation criteria occurred: i.e. when;

- Clear tumour growth (determined to be PD in the RECIST evaluation) or clinical worsening was observed;
- An adverse event was observed that made continued administration difficult;
- An interruption in treatment continued for more than 30 days;
- The patient withdrew consent;
- Continued visits to the hospital became administratively difficult for the patient;
- It became impossible to follow-up the patient;
- Serious or continued non-observance of the protocol occurred;
- The patient became ineligible; or
- The investigator determined that it was necessary to discontinue the study for other reasons.

The study consisted of the following periods:

- Before study period lasted until informed consent was obtained;

- The study period consisted of time from when consent was obtained through to the completion of the post-treatment observation period;
- The administration period consisted of the time during which the investigational drug was administered;
- The recovery period consisted of the time in which the investigational drug was not taken;
- The post-treatment observation period was the 30 days after the final administration of the investigational drug;
- The imaging follow-up examination period was the time from final administration of the investigational drug through to the completion of the imaging follow-up examinations; and
- The survival follow-up period from the date of randomisation until the date of confirmed death.

In the imaging follow-up survey period, imaging was performed according to the study schedule only for patients who discontinued administration of the study drug without confirmation of clear tumour growth (determined to be PD in the RECIST evaluation) or clinical worsening. The image follow-up survey was to be discontinued in the event that any of the following occurred:

- Clear tumour growth or clinical worsening was confirmed and a transition was made to the survival follow-up period;
- Other anti-cancer treatment was started;
- Patient death;
- Patient withdrew consent;
- Impossible to follow up the patient; or
- Other reasons as determined by the investigator.

Survival follow-up was to be discontinued in the event that any of the following items occurred:

- Patient death;
- Patient withdrew consent;
- Impossible to follow up the patient; or
- Other reasons as determined by the investigator.

7.2.2. Inclusion and exclusion criteria

The study included patients aged 20 years with confirmed mCRC who had failed two or more standard chemotherapeutic regimens including fluoropyrimidine, irinotecan, and oxaliplatin.

7.2.3. Treatment

TAS-102 was initially administered at a dose of 70 mg/m^2 per day based on BSA, administered in two equal doses of 35 mg/m^2 within 1 hour of the morning and evening meals. The initial dose was to be administered within 8 days of randomisation, and if the dose could not be administered in this time period then the patient was discontinued from the study. As a rule, there were to be no revisions according to changes in body weight after the start of administration. However, if a change in body weight of 10% or greater was observed compared to randomisation, a dose revision based on BSA was made at the start of the next cycle.

Each cycle was to be 28 days, with the investigational drug (TAS-102 or a placebo) given orally 2 times a day (after morning and evening meals) for 5 consecutive days (Days 1 to 5), followed by a 2 day drug-free period (Days 6 to 7), after which treatment with the investigational drug was repeated for a further 5 consecutive (Days 8 to 12), followed by a 2 day drug-free period (Days 13 to 14), followed by a 14 day recovery period (Days 15 to 28) prior to the start of the next cycle. The

placebo tablets were identical in appearance to TAS-102 and contained all the ingredients except the active drug.

The study included criteria ('standards') for initiating treatment in each cycle, and criteria for interrupting treatment and re-starting treatment. Missed doses were not to be replaced, even in cases where treatment was interrupted and then resumed in the same cycle. In cases where treatment was interrupted and the resumption criteria were not met within the cycle, the next cycle could be started following a treatment interruption of at least 14 days. Treatment interruptions were to be a maximum of 30 consecutive days, with interruptions longer than this resulting in patient discontinuation.

The total daily dose was to be reduced by 10 mg/day beginning at the next cycle if the neutrophil count was under 500/mm^3, the platelet count was under 50,000/mm^3 or whenever the investigator deemed it necessary to reduce the dose for patient safety. The minimum total daily dose was 30 mg, and dose reduction below this level was not permitted. Once a dose had been was reduced, increased doses were not permitted.

Unless deemed necessary, no other anti-cancer drugs, other investigational drugs or other therapies considered to potentially influence the assessment of efficacy or safety of the investigational drugs were permitted during the study. Standard treatments were permitted for the management of major adverse drug reactions, decreased neutrophil counts (for example, G-CSF), decreased platelet counts, nausea, vomiting and fatigue.

7.2.4. Efficacy variables and outcomes

7.2.4.1. Primary efficacy endpoint

The primary efficacy endpoint was overall survival (OS), defined as the time (in months) from randomisation to the date of death from any cause. In the absence of death confirmation, or for patients alive as of the OS cut-off date, survival time was censored at the date of last study follow-up, or the final confirmation date on which survival was confirmed before follow-up became impossible. The primary endpoint of OS was to be analysed when 121 deaths had occurred.

7.2.4.2. Secondary efficacy endpoints

Progression-free survival (PFS) was defined as the time (in months) from randomisation to the date that the patient's condition reached progressive disease (PD). If the patient died before reaching PD, the date of death was considered the date PD was reached. For patients that had not reached PD at the time of the analysis, and for patients for whom the PD date was unknown, PFS was censored at the date of the patient's final assessment prior to data cut-off. The randomisation date was used for cases in which lesion evaluation had not been performed after randomisation, and the initiation date of other (post-treatment) anti-cancer therapy was used when other anti-cancer therapy was initiated before the patient reached PD.

Time to treatment failure (TTF) was defined as the time (in months) from randomisation to the date that PD was confirmed, the date that the study was discontinued, or the date of death if it occurred prior to the date of discontinuation of the study, whichever came sooner. If these criteria were not met, the final evaluation date was to be used in analysis.

Best overall response was determined as CR (complete response), PR (partial response), stable disease (SD), progressive disease (PD) or NE (not evaluable).

Table 39: Best overall response determinations

Overall response	Target lesions	Non-target lesions	New lesions
CR	CR	CR	None
PR	CR	IR/SD	None
PR	PR	Non-PD	None
SD	SD	Non-PD	None

Overall response	Target lesions	Non-target lesions	New lesions
PD	PD	Any	Yes or No
PD	Any	PD	Yes or No
PD	Any	Any	Yes

CR: After initially reaching CR, that condition must be maintained and radiologically confirmed after at least four weeks; PR: After initially reaching PR, the PR condition must be maintained and radiologically confirmed after at least four weeks; SD: The response has not reached CR or PR in radiologic assessments over at least six weeks since the start of study drug administration and it has been confirmed that PD has not occurred; PD: The CR, PR, and SD criteria are not fulfilled and PD is radiologically confirmed in target lesions or non-target lesions, or the appearance of new lesions is confirmed.

If it was not possible to evaluate target lesions, non-target lesions, or the appearance of new lesions, the response was considered NE (not evaluable).

- The disease control rate (DCR) was defined as the percentage of patients in which there was no clear worsening of the clinical condition for six weeks or more after the start of administration in patients in which the best overall response was determined to be CR, PR, or SD.
- The duration of overall response was defined as the period from the day when the overall response is first judged to be CR or PR to the day of confirmation of PD.
- The duration of stable disease was defined as the period from the day of initiation of administration in Course 1 to the day of confirmation of PD.
- The time to tumour response (CR or PR) was defined as the period from the day of initiation of administration in Course 1 to the day when the overall response is first judged to be CR or PR.
- The tumour shrinkage rate.

7.2.5. Randomisation and blinding methods

The study was double blinded, with treatment assignment being blinded to patients, investigators, sub-investigators, clinical research staff, and the sponsor. Following confirmation of eligibility, patients were randomised by the registration centre to the two treatment groups (TAS-102 group and placebo group) at a ratio of 2:1, and stratified according to ECOG performance status (PS: 0 versus 1/2). The study included emergency unblinding procedures.

7.2.6. Analysis populations

The analysis sets were:

- Randomised patients: All randomised patients.
- Eligible patients: Randomised patients who fulfil the inclusion criteria and did not violate the exclusion criteria.
- Full Analysis Set (FAS): Eligible patients to whom the investigational drug was administered at least once with observations after administration.
- Investigational drug administration patients: Randomised patients to whom the investigational drug was administered at least once.

7.2.7. Sample size

The total planned randomised patient sample size was 162 patients, including 108 to the TAS-102 group and 54 to the placebo group. Based on previous clinical data, the sponsor estimated the median survival time (MST) to be 9.0 months for the TAS-102 group and 6.0 months for the placebo group. The sponsor assumed a 12-month registration period, a 12-month follow-up period, a significance level of one-sided 10%, power of 80%, and a total of 162 patients randomised 2:1, respectively, to TAS-102 and placebo, based on a 5% FAS rejection rate.

7.2.8. Statistical methods

7.2.8.1. Main analysis

The main analysis was overall survival (OS) in the (FAS). The OS significance level was set at 10% (one-sided), and a stratified log-rank test was performed to test the superiority of TAS-102 compared to placebo. The survival curves were created using the Kaplan-Meier method, and the median survival times and associated 80% CIs were calculated. The survival data were analysed using a Cox proportional hazards model adjusted by stratification factor, and the HR and associated 80% CI were calculated. In addition, the associated 95% CI was calculated for both the median survival time the HR. Based on the OS assumptions used to estimate the sample size, the number of expected deaths at the completion of the 12-month follow-up period was anticipated to be 121. The main analyses were to be performed when 121 deaths had occurred, which means that follow-up could be longer (18 months at the longest from the end of subject registration) or shorter than the anticipated 12 months. The final statistical analysis was to be undertaken at the point when the survival follow-up period was completed for all patients.

7.2.8.2. Secondary analyses

- The response rate (RR) and associated 95% CI were calculated for each treatment group (FAS), and between group testing was performed using Fisher's exact test.
- The disease control rate (DCR) was analysed using the same method described for the RR.
- The total duration of response (DR), the duration of complete response, and the stable period were calculated in the FAS.
- Progression free analysis (PFS) was analysed using similar methods to those described for OS.
- Time to treatment failure (TTF) was analysed using the same methods as those PFS.

7.2.8.3. Missing data

Missing data were not imputed in the analyses.

7.2.8.4. Changes to the statistical analysis plan

There were a large number of amendments to the initial statistical plan. The amendments have been examined and are considered not to have invalidated the efficacy analysis. The final statistical analysis plan (Version 4.0) was dated 19 August 2011. No amendments to the statistical analysis plan appear to be made after finalisation of the plan.

7.2.9. Participant flow

A total of 172 patients were randomised, including 114 patients to TAS-102 and 58 patients to placebo. In the TAS-102 group, 2 patients were excluded (1 was not eligible after treatment and 1 was discontinued before treatment), while in the placebo group 1 patient discontinued before treatment. The FAS population consisted of 169 patients, including 112 patients in the TAS-102 group and 57 patients in the placebo group. At the clinical cut-off for the final report, 4 patients (all in the TAS-102 group) were continuing treatment and 165 patients (108, TAS-102; 57, placebo) had discontinued treatment. Of the 112 patients (FAS) in the TAS-102 group, 88.4% (n = 99) had discontinued treatment due to disease progression compared to 98.2% (n = 57) of the 47 patients (FAS) in the placebo group.

7.2.10. Major protocol deviations

Protocol deviations were observed in 17 (14.9%) patients enrolled in the TAS-102 group and 7 (12.1%) patients enrolled in the placebo group. The main protocol deviation in both treatment groups was deviation from laboratory study/observation schedules (n = 10 (8.8%), TAS-102; n = 7 (12.1%), placebo)). Other deviations from the protocol in the TAS-102 group were deviation from study regimen (n = 4), deviation from defined group (n = 2), deviation related to obtaining consent (n = 1), and deviation from exclusion criteria. The reported protocol deviations are considered not to have invalidated the efficacy or safety assessment of the study.

7.2.11. Baseline data

The baseline demographic characteristics of the two treatment groups (FAS) in this Japanese study were comparable. The median age of the population was 63.0 years (range: 28, 80 years) in the TAS-102 group and 62.0 years (range: 39, 79 years) in the placebo group, with 57.1% and 49.1% of the patients being male, respectively. The distribution of baseline ECOG PS status (TAS-102 versus placebo) was PS 0 (64.3% versus 61.4%), PS 2 (33.0% versus 36.8%), and PS 3 (2.7% versus 1.8%).

The baseline CRC disease characteristics of the two treatment groups (FAS) were comparable. Colon cancer was reported in 56.3% of patients in the TAS-102 group and 63.2% of patients in the placebo group, with the respective proportions for rectal cancer being 43.8% and 36.8%. The cancer was unresectable in 42.0% of patients in the TAS-102 group and 50.9% of patients in the placebo group, while the respective proportions for recurrent disease were 58.0% and 49.1%. For presence/absence of primary tumour, 'absence' was seen in 95 (84.8%) and 49 (86.0%) patients in the TAS-102 and placebo groups, respectively. Metastases were present in all patients, occurring primarily in the liver and lung.

The distribution of prior therapies in the two treatment groups (FAS) was comparable. In the TAS-102 and placebo groups, respectively, there were 103 (92.0%) and 50 patients (87.7%) with a history of surgery, 54 (48.2%) and 15 (26.3%) patients with a history of post-operative adjuvant chemotherapy, 71 (63.4%) and 36 (63.2%) patients with a history of treatment including anti-EGFR antibody, and 87 (77.7%) and 47 (82.5%) patients with a history of treatment including bevacizumab. Of note, a greater proportion of patients in the TAS-102 group received post-operative adjuvant chemotherapy than in the placebo group. In the TAS-102 and placebo groups, respectively, 2 prior chemotherapy regimens were used in 17 (15.2%) and 13 (22.8%) patients, 3 regimens in 46 (41.1%) and 16 (28.1%) patients, and 4 regimens in 30 (26.8%) and 12 (21.1%) patients. Of note, FOLFOX, FOLFIRI and CPT-11+cetuximab were used in 50% or more patients in each group.

The clinical findings at baseline were similar in both treatment groups (FAS), with symptoms of decreased appetite nausea, vomiting diarrhoea and fatigue being reported in a minority of patients in both groups. Concomitant medications and therapies were comparable for the two treatment groups (FAS), with all patients in both groups one or more concomitant medications.

7.2.12. Results for the primary efficacy outcome (OS)

The results for OS are summarised below.

Table 40: Overall survival (OS), FAS population.

	TAS-102 (n = 112)	Placebo (n = 57)
Death	75 (67.0%)	48 (84.2%)
Censored (survival)	37 (33.0%)	9 (15.8%)
Lost to follow-up	0	0
OS (95% CI), median (months)	9.0 (7.3, 11.3)	6.6 (4.9. 8.0)
Hazard Ratio (95% CI)	0.56 (0.39, 0.81)	
p-value, stratified log-rank test	p = 0.0011	

Comment: In the TAS-102 group, median OS was 2.4 months longer than in the placebo group in the FAS, with the difference in median OS between the two treatment groups being statistically significant. The Kaplan-Meier estimates showed that the percentage of patients surviving at 12 months was 36.7% in the TAS-102 group and 15.8% in the placebo group.

7.2.13. Results for other secondary efficacy outcomes

The median progression-free-survival (PFS) assessed by the independent review committee was 2.0 months in the TAS-102 group compared to 1.0 month in the placebo group (HR = 0.41 (95%

CI: 0.28, 0.59); p < 0.0001, stratified log-rank test). There were 91 PFS events in the TAS-102 group compared to 49 PFS events in the placebo group. The median PFS assessed by investigators was 2.7 months in the TAS-102 group compared to 1.0 month in the placebo group (HR=0.34 (95% CI: 0.24, 0.49); p < 0.0001, stratified log-rank test). There were 109 PFS events in the TAS-102 group compared to 56 PFS events in the placebo arm.

The median time to treatment failure (TTF) assessed by the independent review committee was 1.9 months in the TAS-102 group compared to 1.0 month in the placebo group (HR=0.40 (95% CI: 0.28, 0.56); p < 0.0001, stratified log-rank test).

The response rate (RR = CR+PR), based on the independent review committee assessment, was 0.9% (1/112) in the TAS-102 group and 0.0% (0/57) in the placebo group (p = 1.000, Fisher's exact test).

The disease control rate (DCR = CR+PR+SD), based on the independent review committee assessment was 43.8% (49/112) in the TAS-102 group and 10.5% (6/57) in the placebo group (p < 0.0001, Fisher's Exact test).

7.2.14. Efficacy in age subgroups

The data (D120 Response) included an analysis of efficacy by age subgroup. The results are summarised below.

Table 2: Study J003-10040030; OS by age subgroup, ITT population

Age	TAS-102		Placebo		TAS versus PBO
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
<65	60	8.7 (6.7, 11.8)	34	7.2 (4.1, 8.9)	0.62 (0.39, 1.01)
65 -74	43	9.0 (7.1, 13.6)	18	5.3 (3.4, 7.6)	0.48 (0.25, 0.91)
75 – 84	9	6.1 (1.6, -)	5	7.1 (3.1, -)	0.66 (0.17, 2.62)

Table 42: Study J003-10040030; PFS by age subgroup, ITT population

Age	TAS-102		Placebo		TAS versus PBO
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
<65	60	2.4 (1.9, 3.6)	34	1.0 (1.0, 1.1)	0.39 (0.24, 0.61)
65 -74	43	2.8 (1.9, 4.7)	18	1.0 (1.0, 1.2)	0.25 (0.13, 0.48)
75 – 84	9	1.9 (1.0, 15.5)	5	1.0 (1.0, 4.6)	0.49 (0.15, 1.64)

Comment: Both OS and PFS significantly favoured patients in the < 65 years and 65-74 years subgroups treated with TAS-102 compared with placebo. The number of patients in the 75-84 year subgroups in the two treatment groups is considered too small to make meaningful conclusions about OS and PFS.

7.2.15. Analyses performed across trials (pooled analyses and meta-analyses)

No meta-analyses of pooled analyses.

7.3. Evaluator's conclusions on clinical efficacy

The efficacy of TAS-102 for the proposed indication has been demonstrated in one pivotal, multinational, multicentre, randomised, placebo-controlled, double-blind, Phase III study in a total of 800 patients (RECOURSE), and one supportive, multicentre, randomised, placebo-controlled, double-blind, Phase II study in a total of 172 Japanese patients (Study J003-10040030). Both studies included patients with refractory mCRC who had received at least 2 prior standard chemotherapy regimens, including fluoropyrimidine, irinotecan, and oxaliplatin.

The standard prior chemotherapy regimens used in the studies are consistent with regimens likely to be used in Australia for the treatment of mCRC. However, regorafenib, which is approved in Australia for a similar patient population studied in the pivotal and supportive studies, was not approved in any jurisdiction when the TAS-102 studies were designed. Consequently, there are limited data in the submission on patients previously treated with regorafenib.

In RECOURSE, randomised patients were stratified by KRAS status (wild-type versus mutant), time since diagnosis of metastasis (<18 months versus ≥18 months), and geographic region (Region 1: Asia (Japan) versus Region 2 Western (Australia, Europe, US)). In Study J003-10040030, randomised Japanese patients were stratified by ECOG PS (PS = 0 versus PS = 1 or 2).

In both the pivotal and supportive study, patients were randomised to receive TAS-102 (35 mg/m^2/dose BD) plus BSC or placebo plus BSC for 5 consecutive (Days 1 to 5), followed by 2 rest days (Days 6 to 7), after which treatment was repeated for 5 consecutive days (Days 8 to 12), followed by 2 rest days (Days 13 to 14) and then 14 days recovery (Days 15 to 28). The 28 day treatment cycles were repeated in each study until the pre-specified number of deaths required for the primary analysis of OS occurred. The primary efficacy endpoint in both studies was OS, which is consistent with the relevant TGA adopted EU guidelines for the clinical assessment of anti-cancer medicines (CPMP/EWP/205/95/Rev.3/Corr).

7.3.1. RECOURSE (Pivotal Phase III study)

The patient population treated in RECOURSE is considered to be reasonably representative of the Australian patient population with advanced mCRC likely to be offered treatment with TAS-102 if approved. The median age of the total patient group in RECOURSE was 63.0 years (range: 27 to 82 years), and 44% were aged ≥ 65 years. There were more males than females in the total patient population (61.4% versus 38.6%, respectively). The majority of the population were categorised as Caucasian/White (57.6%), with most of the remaining patients being Asian/Oriental (34.8%). Of the total patient population, 60.9% had been treated with ≥ 4 prior chemotherapy regimens for mCRC.

In RECOURSE, patients with mCRC refractory to standard chemotherapies were randomised to double-blind treatment with TAS-102 plus BSC (n = 534) or placebo plus BSC (n = 266). The primary efficacy analysis was comparison of OS between the two treatment arms, with survival follow-up data being obtained through the date of the 571st death observed in the study. At the cut-off date for the primary analysis of OS (24 January 2014) there had been a total of 574 deaths, including 364 (68.2%) in the TAS-102 arm and 210 (78.9%) in the placebo arm.

The median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The modest increase in OS of 1.8 months in the TAS-102 arm compared to the placebo arm was statistically significant: HR = 0.68 (95% CI: 0.58, 0.81), p < 0.0001 (1 sided and 2 sided), stratified log-rank test. The primary analysis of OS was supported by a number of additional OS analyses, including sensitivity analyses, analyses based on the individual stratification factors and subgroup analyses. The updated OS analysis (as of data cut-off date of 8 October 2014) was based on 712 deaths (463 (86.7%), TAS-102; 249 (93.6%), placebo). In the updated analysis, the median OS was 7.2 months in the TAS-102 arm and 5.2 months in the placebo arm: HR = 0.69 (95% CI: 0.59, 0.81); p<0.0001 (1 and 2-sided), stratified log-rank test. The results of the updated OS analysis were consistent with the results for the primary OS analysis.

The modest improvement in OS in the TAS-102 arm compared to the placebo arm needs to be interpreted in the context of patients with mCRC resistant to standard treatments. Patients were required to have received at least 2 prior regimens of standard chemotherapies for mCRC refractory. Standard chemotherapy must have included all of the following agents approved in each country in which patients were enrolled: fluoropyrimidines, irinotecan and oxaliplatin; an anti-VEGF monoclonal antibody (bevacizumab); and at least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients. Of the total patient population, the proportion of patients who had receive 1, 2, 3 and ≥ 4 prior regimens for mCRC was

3%, 22.8%, 27.8% and 46.5%, respectively. Of the total population, 93.8% were reported as being intolerant to fluoropyrimidine in their last prior regimen.

A limitation of the study relates to the small amounts of data in patients treated with regorafenib, due to the medicine not being approved at the time of the study design. In Australia, the indications of regorafenib include the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Of the total number of patients in the RECOURSE ITT population, 18.0% (n = 144) had previously been treated with regorafenib (17.0% (n = 91) TAS-102; 19.9% (n = 53) placebo). The OS subgroup analyses showed that there was trend towards longer median survival time in patients in the TAS-102 arm compared to the placebo arm, irrespective of whether or not they had received prior treatment with regorafenib.

The Australian PI for regorafenib (Stivarga) indicates that the median OS was 6.4 months in the regorafenib plus BSC group and 5.0 months in the placebo plus BSC group: HR = 0.774 (95% CI: 0.636, 0.942), p=0.005178. The results reported in the PI for OS for regorafenib in heavily pre-treated patients with mCRC refractory to standard chemotherapies are consistent with the results for OS for TAS-102 in RECOURSE in a similar patient population, although cross study results should be interpreted cautiously due to uncertainties relating to the comparability of the treated populations.

The key secondary efficacy endpoint of PFS in the ITT population based on investigator-assessed radiological disease progression undertaken on the specified cut-off date for non-survival data (31 January 2014) demonstrated a median time of 2.0 months in the TAS-102 arm and 1.7 months in the placebo arm. The small increase in median PFS of 0.3 months in the TAS-102 arm compared to the placebo arm was statistically significant: HR = 0.48 (95% CI: 0.41, 0.57), p < 0.0001 (1 sided and 2 sided), stratified log-rank test. The PFS events in both treatment arms were primarily disease progression rather than death. It is possible that the analysis of the PFS might have been subject to bias, as radiological progression was based on investigator-assessment rather than centralised reading. However, the supportive PFS analyses were consistent with the primary PFS analysis as were the PFS analyses by stratification factors and pre-specified subgroups. The other secondary efficacy endpoints of TTF (ITT population), ORR, and time to ECOG status ≥ 2 all favoured the TAS-102 arm compared to the placebo arm with p-values being nominally statistically significant.

RECOURSE included only patients with ECOG PS 0 or 1 (56.0% versus 44.0%, respectively), respectively), and excluded patients with ECOG PS ≥ 2 (that is, patients with more severe impairment in quality of life due to mCRC). The absence of patients with ECOG PS ≥ 2 is considered to be a deficiency in the data. It can be anticipated that in clinical practice, a considerable proportion of patients with refractory mCRC likely to be offered treatment with TAS-102 might be categorised with ECOG PS status ≥ 2. However, an analysis of time to worsening ECOG PS status was pre-specified in the statistical analysis plan for RECOURSE. The median time to ECOG PS ≥ 2 was 5.7 months in the TAS-102 arm and 4.0 months in the placebo arm: HR = 0.66 (95% CI: 0.56, 0.78); p<0.0001, stratified log-rank test. The difference between the 2 treatment arms was 1.7 months in favour of the TAS-102 arm. There were no specific data in the submission assessing patient or investigator reported quality of life (QoL) outcomes in patients with mCRC treated with TAS-102 or placebo. This is a significant deficiency in the submitted data, given the importance of quality of life assessment in patients with cancer being treated with chemotherapy.

7.3.2. Study J003-10040030 (Supportive Phase II study)

At the cut-off date for the OS analysis in Japanese patients, death had occurred in 75 patients in the TAS-102 group (67.0% (75/112)) and 48 patients in the placebo group (84.2% (48/75)). The median OS in the FAS was 9.0 months in the TAS-102 group and 6.6 months in the placebo group: HR=0.56 (95% CI: 0.39, 0.81); p = 0.0011, stratified log-rank test. The difference in median OS between the two treatment groups was 2.4 months in favour of the TAS-102 group. This relatively small improvement in OS should be interpreted in the context of heavily pre-treated patients with refractory mCRC.

The secondary efficacy endpoint of PFS assessed by an independent review committee demonstrated that median PFS was 2.0 months in the TAS-102 group compared with 1.0 month in the placebo group: HR=0.41 (95% CI: 0.28, 0.59); nominal p < 0.0001, stratified log-rank test. The results for the median TTF (secondary efficacy endpoint) assessed by the independent review committee was consistent with results for the PFS. For best tumour response assessed by independent review committee, the ORR (CR+PR) was negligible for both treatment groups (0.9% (1/112), TAS-102 versus 0% (0/57), placebo; nominal p=1.000, Fisher's Exact test). The DCR (CR+PR+SD) assessed by independent review committee was 43.8% (49/112) in the TAS-102 group and 10.5% (6/57) in the placebo group (nominal p < 0.0001, Fisher's Exact test). No statistical adjustments were made for multiple pairwise testing of the secondary efficacy endpoints. Therefore, it is considered that the secondary efficacy endpoints should be considered to be exploratory rather than confirmatory, with all significant p-values being nominal.

8. Clinical safety

8.1. Studies providing evaluable safety data

The key integrated safety data were presented in an Integrated Summary of Safety (ISS) for all patients with mCRC who received TAS-102 at a dose of 35 mg/m^2 BD (Safety Data Group 1; n = 761) and for all patients in the 2 placebo controlled studies (RECOURSE; Study J003-10040030) who received TAS-102 (n = 646) or placebo (Safety Data Group 2; n = 656 (TAS-102), n = 322 (placebo)). The studies included in Safety Data Groups 1 and 2 are summarised below.

Table 43: Overview of clinical studies included in the integrated safety database; patients with mCRC receiving starting dose of TAS-102 35 mg/m^2.

		Number of Treated Patients	
Study Design	**Study Number**	**TAS-102**	**Placebo**
Randomised, placebo-controlled, double-blind	TPU-TAS-102-301 (Phase III, Global[a])	533	265
	J003-10040030 (Phase II, Japan)	113	57
	Total for Safety Data Group 2	**646**	**322**
Open-label	J001-10040010 (Phase I, Japan)	5	---
	J004-10040040 (Phase I, Japan)	5	---
	TPU-TAS-102-101 (Phase I, USA)	24	---
	TPU-TAS-102-102 (Phase I, USA)	29	---
	TPU-TAS-102-103 (Phase I, UK/USA)	33	---
	TPU-TAS-102-104 (Phase I, USA)	19	---
	Total for Safety Data Group 1	**761**	---

Safety Data Group 1 = Integrated TAS-102 studies investigating 35 mg/m2 BD monotherapy in patients with mCRC. Safety Data Group 2 = Integrated randomised placebo-controlled studies comparing TAS-102 35 mg/m^2 with placebo. a. EU, Japan, USA and Australia.

In addition, to Safety Data Groups 1 and 2, the ISS also included Safety Data Groups 3 and 4. Safety Data Group 3 included serious adverse events (non-integrated) from Safety Data Groups 1 and 2, in addition to the following sources at the SAE cut off date of 24 July 2014 (cumulative data except as noted):

- mCRC patients in Group 1 and 2 remaining on TAS-102 35 mg/m^2 BD monotherapy as of study data cutoff dates (incremental data from these dates to 24 July 2014);

- patients in Group 1 and 2 who had diagnoses other than CRC and/or who received treatment other than TAS-102 35 mg/m^2 BD monotherapy; and
- Other non-integrated studies including completed studies in patients who had diagnoses other than CRC and/or who had received treatment other than TAS-102 35 mg/m^2 BD monotherapy, ongoing studies for which a final report had not been generated and investigator-initiated studies. Safety Data Group 4 included post-marketing safety data.

Comment: The pivotal study (RECOURSE) contributed the majority of data to Safety Data Groups 1 and 2. Consequently, the integrated safety data in Safety Data Groups 1 and 2 were consistent with the safety data from RECOURSE. Therefore, the evaluation of safety in this CER focuses on the randomised, placebo-controlled safety data from RECOURSE (TAS-102 (n = 533); placebo (n = 265)). Comparison of the safety data from the TAS-102 and placebo groups from this multinational, multicentre, randomised, double-blind study provides for a relatively unbiased assessment of safety in the two treatment groups.

8.2. Pivotal Phase III Study (RECOURSE) – Safety data

8.2.1. Treatment duration and exposure

Of the 800 randomised patients, 798 received at least one dose of study medication (n = 533 TAS-102); n = 265 (placebo)) and were included in the as-treated (AT) population. All safety summaries in RECOURSE were performed in the AT population. As of the data cut-off date (31 January 2014), the mean duration of treatment was twice as long for patients receiving TAS-102 as for patients receiving placebo (12.65 versus 6.76 weeks, respectively), while the total time on treatment was almost 4 times longer in the TAS-102 group compared to the placebo group (6744 versus 1791 weeks, respectively). The exposure parameters are summarised below.

Table 44: RECOURSE; Total weeks of exposure, AT population

Parameter	TAS-102 (N = 533)	Placebo (N = 265)
Total number of weeks of exposure	6743.6	1791.4
Mean (SD)	12.65 (11.965)	6.76 (6.117)
Median (Min, Max)	6.71 (0.1, 1.78)	5.71 (0.1, 63.7)

In the TAS-102 group, 87.4% (n = 466) of patients initiated at least 2 cycles of treatment, and 43.3% (n = 231) initiated Cycle 3 (following first 8-week tumour assessment per protocol). In the placebo group, 81.1% (n = 215) of patients initiated at least 2 cycles of treatment, while 18.1% (n = 48) initiated Cycle 3. In the TAS-102 group, 22% (n = 117) of patients initiated > 4 cycles of treatment compared to 4.5% (n = 12) of patients in the placebo group. The total number of cycles initiated in the TAS-102 group was 3-times higher than in the placebo group (1828 versus 598, respectively), and the mean (SD) number of cycles initiated was 3.4 (2.56) in the TAS-102 group and 2.3 (1.49) in the placebo group.

In the TAS-102 group, the were 1784 completed cycles, with the mean ± SD number of completed cycles being 3.4 ± 2.58 and the median number being 2.0 (range: 1, 18). In the placebo group, there were 580 completed cycles, with the mean ± SD number of completed cycles being 2.2 ± 1.51 and the median number being 2.0 (range: 1, 16). The number of patients in the TAS-102 and placebo groups, respectively, completing 1 cycle were 526 (98.7%) and 261 (98.5%), completing 2 cycles were 451 (84.6%) and 206 (77.7%), completing 3 cycles were 220 (41.3%) and 44 (16.6%), completing 4 cycles were 184 (34.5%) and 30 (11.3%), and completing > 4 cycles were 117 (22.0%) and 12 (4.5%).

Comment: The total number of weeks of exposure was approximately 4-fold longer in the TAS-102 group than in the placebo group (6743 versus 1791 weeks respectively). No safety

data could be identified in the study report comparing safety outcomes in the two treatment groups adjusted for duration of exposure. The notably longer period of exposure in the TAS-102 group compared to the placebo group should be taken into account when comparing the AE data between the 2 treatment groups.

8.2.2. Dose administered

The mean total dose administered was higher in the TAS-102 group than in the placebo group (2251 versus 1507 mg/m^2, respectively), which was consistent with the greater number of treatment completed cycles in the TAS-102 group compared to the placebo group. The mean relative dose intensity per cycle in both the TAS-102 and placebo groups indicates high compliance with the dosing schedule in both groups (0.886 versus 0.944, respectively). Across all cycles, 94.4% (503/533) of patients in the TAS-102 group and 93.6% (248/265) of patients in the placebo group received ≥ 80% of their target cycle dose.

Table 45: RECOURSE; Cumulative dose and dose intensity, AT population

Parameter	TAS-102 (N = 533)	Placebo (N = 265)
Total dose administered, mg/m^2		
Mean (SD)	2251.2 (1674.53)	1507.2 (1024.17)
Median (Min, Max)	1405.8 (133, 12470)	1361.3 (139, 11021)
Dose intensity, mg/m^2/week		
Mean (SD)	155.05 (19.965)	165.25 (16.517)
Median (Min, Max)	159.63 (33.1, 189.8)	169.23 (34.8, 187.5)
Relative dose intensity [a]		
Mean (SD)	0.886 (0.1141)	0.944 (0.0944)
Median (Min, Max)	0.912 (0.19, 1.08)	0.967 (0.20, 1.07)

Actual dose intensity (calculated over entire duration of cycle) divided by planned dose intensity (175 mg/m^2/week).

8.2.3. Dose reductions and delays in cycle initiation

In the TAS-102 group, a total of 73 (13.7%) patients had dose reductions, consisting of 53 (9.9%) patients with a single dose reduction, 18 (3.4%) patients with 2 reductions, and 2 (0.4%) patients with 3 reductions. In the TAS-102 group, the median number of cycles until the first dose reduction was 3.0 (range: 2 to 13). In the placebo group, 3 (1.1%) patients had a single dose reduction.

Among all TAS-102 cycles initiated (excluding the initial cycle), 45.2% (585/1295) were delayed ≥ 4 days, and 11.7% (151/1295) were delayed ≥ 8 days. In the TAS-102 group, 466 patients initiated at least 2 cycles of treatment. Of these 466 patients, 245 (52.6%) experienced a delay of ≥ 4 days in initiation of at least 1 cycle, and 108 (23.2%) experienced a delay of ≥ 8 days in initiation of at least 1 cycle. In the TAS-102 group, among the patients with cycle delays, the median number of cycles delayed by ≥ 4 days was 2.0 (range: 1, 14), and the median number of cycles delayed by ≥ 8 days was 1.0 (range: 1, 6).

Among all placebo cycles initiated (excluding the initial cycle), 4.5% (15/333) were delayed ≥ 4 days, and 2.4% (8/333) were delayed ≥ 8 days. In the placebo group, 215 patients initiated at least 2 cycles of treatment. Of these 215 patients, 14 (6.5%) experienced a delay of ≥ 4 days, and 8 (3.7%) experienced a delay of ≥ 8 days. In the placebo group, among patients with cycle delays the median number of cycles delayed by ≥ 4 days was 1.0 (range: 1, 2), and the median number of cycles delayed ≥ 8 days was 1.0 (range: 1, 1).

8.2.4. Adverse events

8.2.4.1. Background

Safety assessments included recording of AEs and SAEs from the time the patient signed the consent form through to 30 days after the last dose of study medication (that is, 30 day Safety Follow up Visit) or until the initiation of new anticancer therapy, whichever came first. AEs reported outside of these time intervals were not categorised as AEs, unless considered by the investigator to be causally related to treatment.

Adverse events (AEs) were any untoward medical conditions that occurred in a patient while participating in the clinical study, and did not necessarily have a causal relationship with the use of the product. Treatment emergent adverse events (TEAEs) were AEs that occurred from the initiation of any study medication administration, and did not necessarily have a causal relationship to the use of the study medication. The Common Terminology Criteria for Adverse Events (CTCAE Version 4.03) terms were used to assess severity and provide the grade for each reported AEs.

Symptoms or laboratory or instrumental (for example, electrocardiographic) abnormalities of a pre-existing disease, such as cancer or other disease, were not be considered an AE. However, occurrences of new symptoms as well as worsening of pre-existing medical conditions were considered AEs. In addition, a new laboratory or instrumental abnormality that had a clinical impact on a patient (e.g., resulting in study medication dose reduction, treatment delay, treatment discontinuation, required treatment due to abnormal values, or considered medically important by the investigator) was considered an AE, unless it was considered part of a clinical condition that was already reported as an AE.

The causal relationship of AEs to treatment were categorised (as defined in the protocol) as related or not-related. The definitions have been reviewed and are considered to be standard for clinical trials. The protocol also provided standard criteria for defining outcomes and included standard requirements for following up AEs.

Serious adverse events (SAEs) were defined in the protocol. SAEs were to be reported by the sponsor within 24 hours from the time the investigator first became aware of the event. All SAEs within the follow-up window (for example, within 30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier) established in the protocol were to be reported to the sponsor. SAEs reported outside the follow-up window were to be reported to the sponsor if considered by the investigator to be related to treatment. All deaths occurring through the 30 day follow-up period were to be recorded and reported to the sponsor within 24 hours.

8.2.4.2. Overview of adverse events

The overall incidence of AEs was similar in the TAS-102 and placebo groups (98.3% versus 93.2%, respectively), while the incidence of treatment-related AEs was notably higher in the TAS-102 group than in the placebo group (85.7% versus 54.7%) as was the incidence of Grade ≥ 3 AEs (69.4% versus 51.7%) and treatment-related SAEs (49.0% versus 9.8%). However, SAEs were reported more frequently in the placebo group than in the TAS-102 group (33.6% versus 29.6%), as were AEs leading to discontinuation (13.6% versus 10.3%) and fatal AEs (11.3% versus 3.2%). The high-level summary of AEs is provided below.

Table 46: RECOURSE; Overview of adverse events, AT population

Number (%) of patients	TAS-102 (N = 533)	Placebo (N = 265)
Any adverse event (AE)	524 (98.3)	247 (93.2)
Any treatment related AE	457 (85.7)	145 (54.7)
Any ≥ Grade 3 AE	370 (69.4)	137 (51.7)

Number (%) of patients	TAS-102 (N = 533)	Placebo (N = 265)
Any treatment-related ≥Grade 3 AE	261 (49.0)	26 (9.8)
Any serious AE (SAE)[a]	158 (29.6)	89 (33.6)
Any AE resulting in discontinuation	55 (10.3)	36 (13.6)
Any AE with outcome of death	17 (3.2)	30 (11.3)

a. Per-protocol, death due to disease progression was not reported as an SAE.

8.2.4.3. Adverse events by system organ class (SOC)

AEs reported in ≥ 10% of patients in the TAS-102 group compared to the placebo group by MedDRA SOC group are summarised below.

Table 47: RECOURSE; Adverse events by system, organ, class, AT population

MedDRA SOC	TAS-102 (n = 533); n (%)		Placebo (n = 265); n (%)	
	All grades	≥ Grade 3	All grades	≥ Grade 3
Any adverse event	524 (98.3)	370 (69.4)	247 (93.2)	137 (51.7)
Gastrointestinal disorders	413 (77.5)	64 (12.0)	161 (60.8)	36 (13.6)
General disorders and administration site conditions	373 (70.0)	141 (53.2)	69 (12.9)	36 (13.6)
Blood and lymphatic tissue disorders	304 (57.0)	189 (35.5)	29 (10.9)	11 (4.2)
Investigations	291 (54.6)	149 (28.0)	92 (34.7)	37 (14.0)
Metabolism and nutrition disorders	248 (46.5)	53 (9.9)	104 (39.2)	27 (10.2)
Infections and infestations	144 (27.0)	35 (6.6)	42 (15.8)	13 (4.9)
Respiratory, thoracic, and mediastinal disorders	142 (26.6**)**	29 (5.4)	80 (30.2)	18 (6.8)
Skin and subcutaneous tissue disorders	127 (23.8)	2 (0.4)	48 (18.1)	2 (0.8)
Musculoskeletal and connective tissue disorders	117 (22.0)	15 (2.8))	55 (20.8	8 (3.0)
Nervous system disorders	113 (21.2)	11 (2.1)	52 (19.6)	11 (4.2)
Renal and urinary disorders	70 (13.1)	12 (2.3)	30 (11.3)	8 (3.0)
Hepatobiliary disorders	55 (10.3)	33 (6.2)	28 (10.6)	18 (6.8)

Comment: Of particular note was the high incidence (≥ 50%, any) in the TAS-102 group of gastrointestinal disorders (predominantly nausea, vomiting, diarrhoea, constipation and upper abdominal pain), general disorders and administration site conditions (predominantly fatigue, pyrexia and asthenia), blood and lymphatic disorders (predominantly anaemia and neutropaenia), and investigations (predominantly neutrophil count decreased, white blood cell count decreased, and platelet count decreased).

8.2.4.4. Adverse events (preferred term) regardless of relationship to treatment

AEs reported in ≥ 10% of patients in the TAS-102 group compared with the placebo group are summarised below, along with the AEs reported by ≥ 2% of patients in the TAS-102 group.

Table 48: RECOURSE; Adverse events reported in ≥ 10% of patients in the TAS-102 group by descending order of frequency, AT population

Preferred Term	Number (%) of Patients			
	TAS-102 (N = 533)		Placebo (N = 265)	
Nausea	258	(48.4)	63	(23.8)
Anaemia	214	(40.2)	22	(8.3)
Decreased appetite	208	(39.0)	78	(29.4)
Fatigue	188	(35.3)	62	(23.4)
Diarrhoea	170	(31.9)	33	(12.5)
Neutropaenia	156	(29.3)	0	
Neutrophil count decreased	148	(27.8)	1	(0.4)
Vomiting	148	(27.8)	38	(14.3)
White blood cell count decreased	146	(27.4)	1	(0.4)
Pyrexia	98	(18.4)	37	(14.0)
Asthenia	97	(18.2)	30	(11.3)
Constipation	81	(15.2)	40	(15.1)
Platelet count decreased	81	(15.2)	6	(2.3)
Abdominal pain	79	(14.8)	36	(13.6)
Cough	57	(10.7)	30	(11.3)
Dyspnoea	56	(10.5)	34	(12.8)

Comment: AEs reported in ≥ 5% of patients in the TAS-102 group, and in ≥ 5% more patients than in the placebo group were nausea (48.4% versus 23.8%), anaemia (40.2% versus 8.3%), decreased appetite (39.0% versus 29.4%), fatigue (35.3% versus 23.4%), diarrhoea (31.9% versus 12.5%), neutropaenia (29.3% versus 0%), neutrophil count decreased (27.8% versus 0.4%), vomiting (27.8% versus 14.3%), while blood cell count decreased (27.4% versus 0.4%), asthenia (18.2% versus 11.3%), platelet cell count decreased (15.2% versus 2.3%), thrombocytopaenia (6.9% versus 0.4%), alopecia (6.8% versus 1.1%), and leukopaenia (5.4% versus 0%). No AEs were reported in ≥ 5% of patients in the placebo group, and in ≥ 5% more patients than in the TAS-102 group.

8.2.4.5. Adverse events by maximum CTC grade

In the TAS-102 group versus the placebo group (respectively), 28.9% versus 41.5% of patients had AEs of maximum Grade 1 or 2, 49.5% versus 34.3% of patients had AEs of maximum Grade 3, 16.7% versus 6.0% of patients had AEs of maximum Grade 4, and 3.2% versus 11.3% of patients had fatal AEs. The most frequently reported Grade 3 AEs in the TAS-102 group occurring in ≥ 5% of patients (vs placebo) were anaemia (15.9% versus 2.6%), neutropaenia (13.7% versus 0%), neutrophil count decreased (11.8% versus 0%), and WBC count decreased (9.2% versus 0%). The most frequently reported Grade 4 AEs in the TAS-102 group occurring in ≥ 2% of patients (vs placebo) were neutropaenia (6.4% versus 0%) and neutrophil count decreased (4.1% versus 0%). AEs reported in ≥ 5% of patients in either treatment group by maximum CTC grade are summarised.

8.2.4.6. Treatment related adverse events

Treatment related AEs (all grades) were reported notably more frequently in patients in the TAS-102 group than in the placebo group (85.7% versus 54.7%, respectively). Treatment-related AEs reported in ≥ 10% of patients in the TAS-102 group (vs placebo), in descending order of frequency, were nausea (39.4% versus 10.9%), anaemia (31.5% versus 4.5%), neutropaenia (28.7% versus 0%), neutrophil count decreased (27.2% versus 0.4%), decreased appetite (26.5% versus 11.3%),

WBC decreased (26.3% versus 0.4%), fatigue (24.8% versus 10.2%), diarrhoea (23.6% versus 9.1%), vomiting (20.1% versus 4.5%), platelet count decreased (14.4% versus 1.5%), and asthenia (10.9% versus 4.5%).

Treatment-related AEs of ≥ Grade 3 severity were reported notably more frequently in patients in the TAS-102 group than in the placebo group (49.0% versus 9.8%). Treatment-related AEs of Grade ≥ 3 severity reported in ≥ 5% of patients in the TAS-102 group (vs placebo), in descending order of frequency, were neutropaenia (20.1% versus 0%), neutrophil count decreased (15.6% versus 0%), anaemia (12.2% versus 1.9%), and WBC decreased (9.8% versus 0%).

8.3. Deaths and other serious AEs

8.3.1. Deaths

8.3.1.1. Fatal AEs

Fatal AEs were reported in 3.2% (n = 17) of patients in the TAS-102 group and 11.3% (n = 30) of patients in the placebo group. The most frequent fatal AE in both treatment groups was general physical health deterioration, which was reported in 6 patients (1.1%) in the TAS-102 group, and 8 (3.0%) patients in the placebo group. In the TAS-102 group, 2 patients died due to hepatic failure, and 2 died due to acute renal failure. In the placebo group, 6 patients died due to hepatic failure, 1 died due to renal failure and 1 died due to renal impairment. 1 patient in the TAS-102 group and 4 patients in the placebo group had fatal AEs of dyspnoea. All other fatal AEs occurred in 1 patient each. The only treatment-related death was a patient in the TAS-102 group who died due to *Klebsiella* pneumonia/septic shock.

Comment: The number fatal AEs reported in the TAS-102 groups was consistent for RECOURSE (n = 17, 3.2%), integrated safety data Group 2 (n = 18, 2.8%) and integrated data group 1 (n = 20, 2.6%). In integrated safety data Group 2, 18 (2.8%) patients in the TAS-102 group and 30 patients (9.3%) in the placebo group experienced fatal adverse events. The most frequent fatal AE in both treatment groups was general physical health deterioration: 6 patients (0.9%) in the TAS-102 group, and 8 (2.5%) patients in the placebo group. In the TAS-102 group, 2 patients died due to hepatic failure, and 2 died due to acute renal failure. In the placebo group, 6 patients died due to hepatic failure, 1 died due to renal failure, and 1 died due to renal impairment. One patient in the TAS-102 group and 4 patients in the placebo group had fatal AEs of dyspnoea. All other fatal events occurred in 1 patient in either treatment group. One fatal (Grade 5) AE in the TAS-102 group (septic shock) was considered related to study medication. In integrated Safety Data Group 1, fatal AEs were reported for 20 (2.6%) patients in the TAS-102 group. In addition to the fatal AEs reported in the TAS-102 group in Safety Data Group 2, additional fatal AEs reported in Group 1 included haematochezia, staphylococcal infection, and an additional case of septic shock (1 patient each). These additional fatal (Grade 5) AEs were not considered related to study medication.

8.3.1.2. All reported deaths ITT population

Fatal AEs are summarised.

Table 49: RECOURSE; Fatal adverse events, AT population

MedDRA SOC Preferred Term	Number (%) of Patients			
	TAS-102 (N = 533)		Placebo (N = 265)	
Respiratory, thoracic and mediastinal disorders	**4**	**(0.8)**	**7**	**(2.6)**
Dyspnoea	1	(0.2)	4	(1.5)
Pleural effusion	1	(0.2)	1	(0.4)

MedDRA SOC Preferred Term	Number (%) of Patients	
	TAS-102 (N = 533)	Placebo (N = 265)
Pulmonary congestion	0	1 (0.4)
Pulmonary embolism	1 (0.2)	0
Pulmonary oedema	1 (0.2)	0
Respiratory arrest	0	1 (0.4)

1 patient had fatal AEs of cardio-respiratory arrest, acidosis, haemorrhage intracranial and renal failure; 1 patient had fatal AEs of abdominal pain, hepatic failure and hepatic encephalopathy. 1patient had fatal AEs of haematemesis and jaundice; 1 patient had fatal AEs of general physical health deterioration and cognitive disorder.; 1 patient had fatal AEs of liver abscess and sepsis.

As of the cut-off date for the non-survival data (31 January 2014), deaths had been reported in 68.9% (n = 368) of patients in the TAS-102 group and 79.7% (n = 212) of patients in the placebo group. The reported deaths included 2 patients who were randomised but not treated. In the treatment period (that is, within 30 days after last dose), there 35 (6.6%) deaths in the TAS-102 group and 33 (12.4%) deaths in the placebo group and these deaths were primarily due to disease progression. As discussed above, the sponsor considered 1 death in the TAS-102 group as being due to drug-related septic shock. All deaths reported in the ITT population are summarised below.

Table 50: RECOURSE; All reported deaths, ITT population

Time point category of deaths	TAS-102 (n = 534); n (%)	Placebo (n = 266); n (%)
All Deaths	368 (68.9)	212 (79.7)
Death after first dose and ≤ 30 days after last dose	35 (6.6%)	33 (12.4%)
Radiologic Disease Progression	10 (1.9)	10 (3.8)
Clinical Disease Progression	18 [a] (3.4)	21 (7.9)
Toxicity	1 [a] (0.2)	0
Other [d]	6 (1.1)	2 (0.8)
Death of patients randomised but not treated		
Not Collected	1 (0.2) [b]	1 (0.2) [c]
Death > 30 days after last dose		
Not Collected	332 (62.2)	178 (66.9)

a. 1 patient died due to *Klebsiella* pneumonia/septic shock considered related to study medication; however, the Investigator indicated clinical disease progression as the primary category of death; b. 1 patient discontinued prior to receiving treatment due to an AE of ascites; c. 1 patient was found to be ineligible for the study; d. 'Other' deaths in the TAS-102 group included: radiologic progression (25 days after discontinuing, 25 days after last dose); ongoing AE of *Staphylococcus* pneumonia (not related) at the time of deaths considered by the investigator to be a symptom of disease progression; fatal; *Staphylococcus* pneumonia (not related); withdrawn consent after Cycle 1, Day 4 (no AE reported, death notified by a family member); fatal AE of pulmonary oedema (not related); fatal AE of pulmonary embolism (not related). 'Other' deaths in the placebo group were fatal AE respiratory arrest (not related) and fatal AEs cardio-respiratory arrest, acidosis, intracranial haemorrhage, and renal failure (not related).

8.3.2. Serious adverse events (SAEs)

SAEs were reported in 29.6% (n = 158) of patients in the TAS-102 group and 33.6% (n = 89) of patients in the placebo group, while treatment-related SAEs were reported in 9.4% (n = 50) of patients in the TAS-102 group and 0.4% (n = 1) of patients in the placebo group.

SAEs reported in ≥ 1% of patients in the TAS-102 group (vs placebo), in descending order of frequency, were general physical health deterioration (2.8% versus 4.2%), febrile neutropaenia

(2.6% versus 0%), anaemia (1.9% versus 0%), abdominal pain (1.5% versus 1.9%), vomiting (1.3% versus 0%), and pulmonary embolism (1.1% versus 0%).

SAEs considered to be treatment-related and reported in ≥ 0.4% (n = 2) of patients in the TAS-102 group (vs placebo), in descending order of frequency, were febrile neutropaenia (2.6% versus 0%), anaemia (1.5% versus 0%), neutropaenia (0.8% versus 0%), vomiting (0.8% versus 0%), pneumonia (0.6% versus 0%), leukopaenia (0.4% versus 0%), abdominal pain (0.4% versus 0%), diarrhoea (0.4% versus 0%), fatigue (0.4% versus 0%), and decreased appetite (0.4% versus 0%).

Comment: The SAE profiles in the TAS-102 groups were consistent in RECOURSE and the integrated safety data Groups 1 and 2. In integrated safety data Group 2, SAEs were reported in 179 (27.7%) patients in the TAS-102 group and 94 (29.2%) patients in the placebo group, with the patient incidence of treatment-related SAEs being 9.8% (n = 63) and 0.6% (n = 2), respectively. In integrated safety data Group 1, SAEs were reported in 202 (26.5%) patients in the TAS-102 group, with the patient incidence of treatment-related SAEs being 9.2% (n = 70).

8.3.3. Adverse events leading to discontinuation

Based on the AE page of the eCRF, 10.3% (n = 55) of patients in the TAS-102 group and 13.6% (n = 36) of patients in the placebo group had AEs leading to discontinuation of study treatment. In contrast to the AE page of the eCRF, based on the treatment discontinuation page of the eCRF only 3.6% (n = 19) of patients in the TAS-102 group and 1.5% (n = 4) of patients in the placebo group had adverse event/SAE indicated as the primary reason for discontinuation. The sponsor states that the discrepancy between the two pages is attributable to the fact that AEs that were symptoms of disease progression were assessed as leading to treatment discontinuation on the AE page of the eCRF, while the patient was reported as having discontinued due to disease progression on the treatment discontinuation page of the eCRF. The distribution of the 55 patients in the TAS-102 group and the 36 patients in the placebo group reported to have discontinued are summarised below. The percentage given for discontinuations due to adverse event/SAE (34.5%, TAS-102; 11.1%, placebo) are based on the total number of patients discontinuing rather than the total number of as-treated patients in the treatment groups.

Table 51: RECOURSE; Number (%) of patients with AEs leading to discontinuation (per adverse event eCRF), AT population

	TAS-102 (n = 55); n (%)		Placebo (n = 36); n (%)	
Primary reason (per eCRF)	All grades	≥ Grade 3	All grades	≥ Grade 3
Adverse event/SAE	19 (34.5)	15 (27.3)	4 (11.1)	3 (8.3)
Clinical disease progression	33 (60.0)	29 (52.7)	30 (83.3)	27 (75.0)
Radiologic progression	3 (5.5)	1 (1.8)	2 (5.6)	0
Patient withdrew consent	0	0	0	0
Death	0	0	0	0
Other	0	0	0	0

Adverse events/SAEs reported as the primary reason for discontinuation in ≥ 2 patients (≥ 0.4%) in the TAS-102 group (n = 533) compared to the placebo group (n = 265), were fatigue (0.8% (n = 4) versus 0% (n = 0)), anaemia (0.4% (n = 2) versus 0% (n = 0)), diarrhoea (0.4% (n = 2) versus 0% (n = 0)), ileus (0.4% (n = 2) versus 0% (n = 0)), general physical health deterioration (n = 2 (0.4% versus n = 1 (0.4%)). Discontinuations with the primary reason given as adverse event/SAE in patients in the TAS-102 group (3.6% (19/533)) and the placebo group (1.5% (4/265)) are summarised. It should be noted that the percentages provided for discontinuations due to adverse event/SAE presented, are based on the total number of patients discontinuing rather than the total number as-treated patients.

8.3.4. Adverse events leading to interruption/delay or reduction of study medication

AEs (all Grades) resulting in dose reduction were reported in 13.5% (n = 72) of patients in the TAS-102 group and 0.8% (n = 2) of patients in the placebo group, with the majority of events being characterised as Grade ≥ 3 AEs (12.0% (n = 64) in the TAS-102 group versus 0.8% (n = 2) in the placebo group). AEs (all Grades) resulting in dose reduction reported in ≥ 1% of patients in the TAS-102 group (vs placebo), in descending order of frequency, were neutropaenia (3.2% (n = 17) versus 0% (n = 0)), anaemia (2.1% (n = 11) versus 0.4% (n = 1)), febrile neutropaenia (1.9% (n = 10) versus 0% (n = 0)), neutrophil count decreased (1.9% (n = 10) versus 0% (n = 0)), fatigue (1.5% (n = 8) versus 0% (n = 0)), and diarrhoea (1.3% (n = 7) versus 0% (n = 0)).

AEs resulting in interruption/delay or reduction of study medication were reported in 54.2% (n = 289) of patients in the TAS-102 group and 13.6% (n = 36) of patients in the placebo group, with the majority of events in both treatment groups being characterised as Grade ≥ 3 AEs (38.5% (n = 205) in the TAS-102 group versus 8.7% (n = 23) in the placebo group). AEs (all Grades) resulting in interruption/delay or reduction of study medication reported in ≥ 1% of patients in the TAS-102 group (vs placebo), in descending order of frequency, were neutrophil count decreased (20.5% (n = 109) versus 0.4% n = 1)), neutropaenia (19.9% (n = 106) versus 0% (n = 0)), anaemia (5.4% (n = 29) versus 0.8% (n = 2)), fatigue (3.0% (n = 16) versus 0.4% (n = 1)), pyrexia (2.8% (n = 15) versus 1.1% (n = 3)), diarrhoea (2.4% (n = 13) versus 0% (n = 0)), febrile neutropaenia (2.1% (n = 11) versus 0% (n = 0)), nausea (1.9% (n = 10) versus 0.4% (n = 1)), vomiting (1.9% (n = 10) versus 0% (n = 0)), decreased appetite (1.7% (n = 9) versus 1.9% (n = 5)), WBC decreased (1.5% (n = 8) versus 0% (n = 0)), asthenia (1.3% (n = 7) versus 0.8% (n = 2)), platelet count decreased (1.3% (n = 7) versus 0% (n = 0)), and abdominal pain (1.1% (n = 6) versus 0.8% (n = 2)).

8.3.5. Other adverse events of interest

8.3.5.1. Background

Additional pre-specified analyses of AEs were performed by the sponsor for the following events of interest, hepatobiliary abnormality-related AEs, renal abnormality-related AEs, haematologic impairment-related AEs, and infection-related AEs. These analyses were based on a list of MedDRA terms selected *a priori* by the sponsor. In addition to pre-specified AEs of interest, the sponsor also examined *ad hoc* AEs of interest consisting of bleeding events, thromboembolic events, cardiac events, and diarrhoea, nausea and vomiting.

8.3.5.2. Hepatobiliary abnormality related adverse events

Hepatobiliary abnormality-related AEs (all Grades) were reported in a similar proportion of patients in the TAS-102 group and in the placebo group (28.1% versus 29.8%). The percentage of patients who discontinued treatment due to hepatobiliary related AEs was higher in the placebo group than in the TAS-102 group (1.5% versus 6.0%, respectively), as was the percentage of patients with fatal AEs in this grouping (2.6% versus 0.6%, respectively). Hepatobiliary abnormality related AEs are summarised below.

Table 52: RECOURSE; Sponsor-defined hepatobiliary abnormality-related adverse events, AT population.

	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
Category – Preferred term	**All Grades**	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Any hepatobiliary abnormality-related AE	**150 (28.1)**	**75 (14.1)**	**79 (29.8)**	**48 (18.1)**
AEs resulting in treatment discontinuation	**8 (1.5)**	**6 (1.1)**	**16 (6.0)**	**13 (4.9)**
Fatal AEs	3 (0.6)	3 (0.6)	7 (2.6)	7 (2.6)
Hepatic failure	2 (0.4)	2 (0.4)	6 (2.3)	6 (2.3)
Jaundice	0	0	1 (0.4)	1 (0.4)
Liver abscess	1 (0.2)	1 (0.2)	0	0

Category – Preferred term	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Hepatic encephalopathy	0	0	1 (0.4)	1 (0.4)

8.3.5.3. Renal abnormality-related adverse events

Renal abnormality-related AEs (all Grades) were reported more frequently in the TAS-102 group than in the placebo group (9.0% versus 4.9%, respectively). Renal abnormality-related AEs resulting in treatment discontinuation occurred infrequently in both treatment groups (0.4% both groups), as did fatal AEs (0.4% (TAS-102); 0.8% (placebo)). Renal abnormality-related AEs are summarised below.

Table 53: RECOURSE; Sponsor defined renal abnormality-related adverse events, AT population

Category – Preferred term	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any renal abnormality-related AE	48 (9.0)	6 (1.1)	13 (4.9)	3 (1.1)
Proteinuria	22 (4.1)	0	5 (1.9)	0
Blood creatinine increased	18 (3.4)	1 (0.2)	7 (2.6)	1 (0.4)
Renal failure acute	5 (0.9)	5 (0.9)	0	0
Blood urea increased	2 (0.4)	0	1 (0.4)	0
Urine output decreased	1 (0.2)	0	0	0
Renal failure	1 (0.2)	1 (0.2)	1 (0.4)	1 (0.4)
Renal impairment	1 (0.2)	0	1 (0.4)	1 (0.4)
AEs resulting in treatment discontinuation	2 (0.4)	1 (0.2)	1 (0.4)	1 (0.4)
Blood creatinine increased	1 (0.2)	0	0	0
Renal failure acute	1 (0.2)	1 (0.2)	0	0
Renal impairment	0	0	1 (0.4)	1 (0.4)
Fatal AEs	2 (0.4)	2 (0.4)	2 (0.8)	2 (0.8)
Renal failure	0	0	1 (0.4)	1 (0.4)
Renal failure acute	2 (0.4)	2 (0.4)	0	0
Renal impairment	0	0	1 (0.4)	1 (0.4)

Comment: The most notable difference in renal abnormality-related AEs related to an increased incidence of proteinuria in the TAS-102 group compared to the placebo group.

8.3.5.4. Haematologic impairment-related adverse events

Haematologic impairment-related AEs (all Grades) were reported notably more frequently in the TAS-102 group than in the placebo group (70.9% versus 15.5%), as were Grade ≥ 3 AEs in this grouping (46.5% versus 5.7%). However, haematologic impairment-related AEs resulting in treatment discontinuation and death were infrequent in both treatment groups. Haematologic impairment-related AEs are summarised below.

Table 54: RECOURSE; Sponsor defined haematologic impairment-related adverse events, AT population

Category – Preferred term	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any haematologic impairment-related AE [a]	378 (70.9)	248 (46.5)	41 (15.5)	15 (5.7)
Anaemia	214 (40.2)	86 (16.1)	22 (8.3)	7 (2.6)

Category – Preferred term	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Neutropaenia	156 (29.3)	107 (20.1)	0	0
Thrombocytopaenia	37 (6.9)	11 (2.1)	1 (0.4)	1 (0.4)
Leukopaenia	29 (5.4)	13 (2.4)	0	0
Febrile neutropaenia	20 (3.8)	20 (3.8)	0	0
AEs resulting in treatment discontinuation	3 (0.6)	3 (0.6)	0	0
Anaemia	2 (0.4)	2 (0.4)	0	0
Disseminated intravascular coagulation	1 (0.2)	1 (0.2)	0	0
Neutropaenia	1 (0.2)	1 (0.2)	0	0
Fatal AEs	1 (0.2)	1 (0.2)	0	0
Septic shock	1 (0.2)	1 (0.2)	0	0

Haematologic impairment-related AEs (all Grades) reported in ≥ 1% of patients in the TAS-102 group; all other AEs in this grouping in the TAS-102 group were reported in < 1%.

Comment: Haematologic impairment-related AEs are the major safety concern associated with TAS 102 treatment for the proposed indication. However, most of the AEs in this grouping were manageable by dose interruptions/delays or dose reductions rather than treatment discontinuation. Blood transfusions were received by 16.9% (n = 90) of patients in the TAS-102 group and 3.0% (n = 8) of patients in the placebo group. The percentage of patients in the TAS-102 group who received blood transfusions is consistent with the percentage of patients in the group with Grade ≥ 3 anaemia based on haematologic laboratory results. Other anti-anaemic preparations (darbepoetin alfa, epoetin alfa, erythropoietin, livalavin, others) were received by 4.7% (n = 25) of patients in the TAS=102 group and 0.4% (n = 1) patient in the placebo group. Granulocyte colony stimulating factors (G-CSF) were used as supportive therapy during the study in 9.4% (n = 50) patients in the TAS-102 group and no patients in the placebo group. Concentrated platelets/thrombocytes were received by 0.6% (n = 3) of patients in the TAS-102 group during the study and 0.4% (n = 1) of patients in the placebo group.

8.3.5.5. Infection-related adverse events

Infection-related AEs (all Grades) occurred notably more commonly in the TAS-102 group compared to the placebo group (73.7% versus 33.2%, respectively), as did Grade ≥ 3 AEs in this grouping (45.2% versus 14.0%). AEs (all Grades) in this grouping resulting in treatment discontinuation were infrequent in both treatment groups (1.1% (TAS-102); 3.0% (placebo)). There were 3 deaths in the TAS-102 group relating to infection-related AEs and no deaths in the placebo group due to this AE grouping. Infection-related AEs are summarised below.

Table 55: RECOURSE; Sponsor defined haematologic impairment-related adverse events, AT population

Category – Preferred term	TAS-102 (n = 533), n (%)		Placebo (n = 265); n (%)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Any infection related AE [a]	**393 (73.7)**	**241 (45.2)**	**88 (33.2)**	**37 (14.0)**
Nasopharyngitis	23 (4.3)	0	4 (1.5)	0
Urinary tract infection	18 (3.4)	3 (0.6)	5 (1.9)	3 (1.1)
Upper respiratory tract infection	17 (3.2)	0	4 (1.5)	0
Bronchitis	8 (1.5)	1 (0.2)	2 (0.8)	0
Herpes zoster	8 (1.5)	1 (0.2)	0	0
Biliary tract infection	7 (1.3)	5 (0.9)	1 (0.4)	1 (0.4)
Pneumonia	6 (1.1)	4 (0.8)	4 (1.5)	1 (0.4)
AEs resulting in treatment discontinuation	**6 (1.1)**	**5 (0.9)**	**8 (3.0)**	**5 (1.9)**
Fatal AEs	3 (0.6)	3 (0.6)	0	0
Liver abscess	1 (0.2)	1 (0.2)	0	0
Pneumonia staphylococcal	1 (0.2)	1 (0.2)	0	0
Sepsis	1 (0.2)	1 (0.2)	0	0
Septic shock	1 (0.2)	1 (0.2)	0	0

Infection-related AEs (all Grades) reported in ≥ 1% of patients in the TAS-102 group; all other AEs in this grouping in the TAS-102 group were reported in < 1%.

8.3.5.6. Bleeding events

Bleeding AEs (all Grades) were reported in a similar proportion of patients in the TAS-102 and placebo groups (8.1% versus 8.7%, respectively), while ≥ Grade 3 AEs were reported in 3.0% of patients in the placebo group and 0.6% of patients in the TAS-102 group. The most frequently reported bleeding events (all grades) in patients (≥ 1%) in the TAS-102 group (versus placebo) were rectal haemorrhage (1.3% versus 0.4%) and epistaxis (1.7% versus 2.3%). The three Grade ≥ 3 bleeding events reported in the TAS-102 group were 2 of peritoneal haemorrhage and 1 of haematuria, and the eight Grade ≥ 3 bleeding events reported in the placebo group were 3 of haematuria, 2 of haematemesis, and 1 each of gastrointestinal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.

Comment: The results indicate that the notably higher incidence of anaemia observed in the TAS-102 group compared to the placebo group is due to myelosuppression rather than bleeding.

8.3.5.7. Thromboembolic events (arterial or venous)

Thromboembolic events (arterial or venous), all Grades, were reported more frequently in patients in the TAS-102 group than in the placebo group (3.9% versus 1.5%, respectively), and the majority of events were ≥ Grade 3 in severity (2.1% versus 1.5%, respectively). The major difference between the two treatment groups was due to the higher incidence of pulmonary embolism (all Grades) in patients in the TAS-102 group compared to the placebo group (1.7% (n = 9) versus 0% (n = 0)). All pulmonary embolisms in the TAS-102 group were ≥ Grade 3 in severity, including one fatal event. Of the 9 events of pulmonary embolism in the TAS-102 group, 7 (including the 1 fatal event) were reported as being unrelated to study medication. The single death reported by an investigator to be due to pulmonary embolism occurred at home, without documented radiologic diagnosis of DVT or pulmonary embolism and without AEs suggestive of thromboembolism occurring prior to the fatal event. 5 of the 9 cases of pulmonary embolism resolved without ongoing complications. Despite the higher patient incidence of pulmonary embolism in the TAS-102 group

compared to the placebo group, deep vein thrombosis (all Grades) was reported in a similar proportion of patients in the two treatment groups (0.6% (n = 3) TAS-102; 0.8% (n = 2) placebo).

The sponsor identifies three factors that it considers might have contributed to the imbalance in the patient incidence of pulmonary embolism between the two treatment groups. These were : (1) More chest CT scans were undertaken in the TAS-102 group than in the placebo group, due to more patients in the TAS-102 group remaining on study medication beyond 2 cycles compared to the placebo group (that is, 43.3% versus 18.1%, respectively). As chest CT scans were mandated by the protocol to be undertaken every 2 cycles, there were more post-baseline chest CT scans undertaken in the TAS-102 group than in the placebo group increasing the chance of detecting pulmonary embolism. (2) The absence of pulmonary embolism in the placebo arm is inconsistent with the expected frequency of thromboembolic events in patients with colorectal cancer. Therefore, the absence of pulmonary embolism might have been a chance finding. (3) There was no imbalance between the two treatment groups in the proportion of patients with DVT, even though the total time on treatment was nearly 4-fold greater for patients in the TAS-102 group compared to the placebo group. The sponsor comments that a 'true increase in (pulmonary embolisms) would be expected to be accompanied by an increase in the rate of DVTs'.

8.3.5.8. Cardiac adverse events

The proportion of patients in the two treatment groups with any cardiac arrhythmic or cardiac ischaemic event (all Grades) was similar in the TAS-102 and placebo groups (3.2% versus 3.8%, respectively), as was the proportion of patients with ≥ Grade 3 AEs (0.6% versus 0.8%, respectively). There were 15 (2.8%) patients in the TAS-102 group with any arrhythmic event compared to 9 (3.4%) patients in the placebo group. Cardiac AEs (all Grades) reported by ≥ 2 patients in the TAS-102 group (vs placebo) were sinus tachycardia (n = 5 (0.9%) versus n = 3 (1.1%)), right bundle branch block (n = 2 (0.4%) versus 0% (n = 0)), tachycardia (n = 2 (0.4%) versus n = 4 (1.5%)), sinus and bradycardia (n = 2 (0.4%) versus 0% (n = 0)). There were 3 (0.6%) patients in the TAS-102 group with ischaemic events (1 each for acute myocardial infarction, angina pectoris, and troponin increased) compared to 1 (0.4%) patient in the placebo arm (1 myocardial ischaemia).

8.3.5.9. Diarrhoea, nausea and vomiting

AEs of diarrhoea, nausea and vomiting (all Grades) occurred notably more frequently in patients in the TAS-102 group than in the placebo group (62.3% versus 38.1%, respectively), as did ≥ Grade 3 AEs (5.6% versus 1.9%, respectively). In the TAS-102 group, nausea alone occurred more frequently than diarrhoea alone, which in turn occurred more frequently than vomiting alone. The results for nausea, vomiting and diarrhoea are summarised below.

Table 56: RECOURSE;Adverse events of diarrhoea, nausea and vomiting, AT population

	TAS-102 (n = 533); n (%)				Placebo (n = 265); n (%)			
Preferred term	**All Grades**		**≥ Grade 3**		**All Grades**		**≥ Grade 3**	
Diarrhoea and/or nausea and/or vomiting	332	(62.3)	30	(5.6)	101	(38.1)	5	(1.9)
Diarrhoea alone	49	(9.2)	15	(2.8)	19	(7.2)	1	(0.4)
Nausea alone	87	(16.3)	4	(0.8)	37	(14.0)	3	(1.1)
Vomiting alone	14	(2.6)	4	(0.8)	18	(6.8)	1	(0.4)
Diarrhoea and nausea (no vomiting)	48	(9.0)	0		7	(2.6)	0	
Diarrhoea and vomiting (no nausea)	11	(2.1)	1	(0.2)	1	(0.4)	0	
Nausea and vomiting (no diarrhoea)	61	(11.4)	6	(1.1)	13	(4.9)	0	
Diarrhoea, nausea and vomiting (all 3	62	(11.6)	0		6	(2.3)	0	

Concomitant anti-diarrhoeal therapies were used in 22.9% (n = 122) of patients in the TAS-102 group and 14.0% (n = 37) of patients in the placebo, including anti-propulsive medicines

(predominantly loperamide and lomotil) in 18.6% (n = 99) and 8.7% (n = 23) of patients, respectively. Concomitant anti-emetic therapies were used in 30.4% (n = 162) of patients in the TAS-102 group and 30.6% (n = 81) of patients in the placebo group. Concomitant anti-emetic therapies in patients with nausea/vomiting were used in 40.6% (115/283) of patients in the TAS-102 group and 48.8% (40/82) in the placebo group.

8.4. Clinical laboratory tests

8.4.1. Haematology

8.4.1.1. CTC Grade 3 or 4 abnormalities

Per-protocol, haematology tests were performed at Week 2 (Day 15) and Week 4 (prior to start of next cycle) during each treatment cycle. Based on clinical laboratory assessments, 200 (37.9%) patients in the TAS-102 group experienced Grade 3 or Grade 4 neutropaenia and 113 (21.4%) patients experienced Grade 3 or 4 leukopaenia during treatment, while no Grade 3 or 4 AEs were observed for these parameters in the placebo group. Grade 3 or 4 lymphocytopaenia, anaemia and thrombocytopaenia were all reported more frequently in the TAS-102 group than in the placebo group. The results for maximum Grade 3 or 4 haematology laboratory test abnormalities are summarised below.

Table 57: RECOURSE; Grade 3 or 4 abnormalities in haematology parameters that worsened from Baseline, AT population

	TAS-102 (n = 533)			Placebo (n = 265)		
Abnormality	**N [a]**	**Grade 3, n (%)**	**Grade 4, n (%)**	**N [a]**	**Grade 3, n (%)**	**Grade 4, n (%)**
Leukopaenia	528	98 (18.6)	15 (2.8)	263	0	0
Neutropaenia	528	140 (26.5)	60 (11.4)	263	0	0
Lymphocytopaenia	522	95 (18.2)	17 (3.3)	262	24 (9.2)	2 (0.8)
Anaemia	528	96 (18.2)	--- [b, c]	263	8 (3.0)	--- [b]
Thrombocytopaenia	528	24 (4.5)	3 (0.6)	263	0	1 (0.4)

Denominator for percentages: number of patients with at least one post-baseline measurement during treatment (includes patients with missing baseline). There is no CTC Grade 4 for anaemia based on laboratory data only. One adverse event of Grade 4 anaemia was reported.

8.4.1.2. Neutrophil counts

During Cycle 1, median neutrophil counts at Week 2 were 3.40 x 10^9/L in the TAS-102 group and 4.71 x 10^9/L in the placebo group. At Week 4, median neutrophil counts were 2.70 x 10^9/L in the TAS-102 group and 4.98 x 10^9/L in the placebo group. Among patients in the TAS-102 group who experienced Grade 3 or Grade 4 neutropaenia during Cycle 1 (n = 39), the counts at nadir (based on all measurements obtained) ranged from 0.034 to 0.960 x 10^9/L (median = 0.527 x 10^9/L).

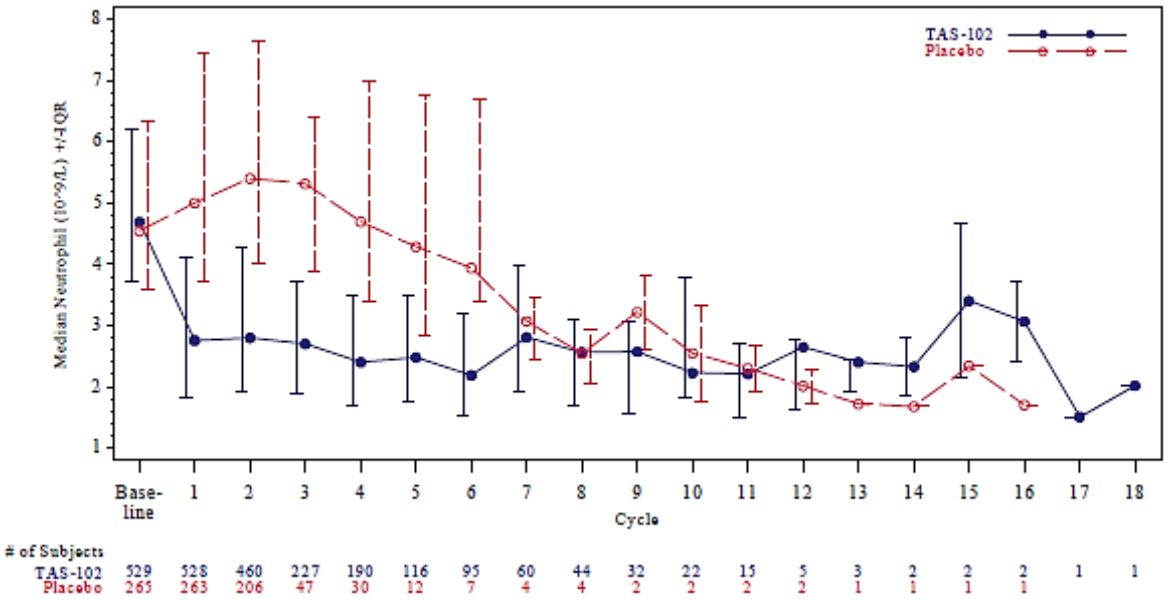
Among all patients with Grade 3 or 4 neutropaenia in the TAS-102 group, median time to recovery (that is, to Grade <2 or ≤ baseline grade) from the most extreme counts recorded was 8 days. Among the 60 patients in the TAS-102 group who experienced Grade 4 neutropaenia, the event was observed in a total of 87 cycles. For 62 of the 87 occurrences of Grade 4 neutropaenia (71.3%), the neutrophil count recovered to < Grade 4 within 7 days. However, analyses of time to recovery in haematology parameters were limited by the fact that the protocol mandated haematology testing only on Week 2 and Week 4 of each cycle.

Among the 87 occurrences of Grade 4 neutropaenia in the TAS-102 group, 10 cases had associated AEs of febrile neutropaenia defined as occurring within ±7 days of Grade 4 neutropaenia, 8 cases

were associated with other AEs of fever, and 12 cases were associated with various infections. 22 of the 87 cases had associated administration of G-CSF/GM-CSF, and 27 of the 87 cases had associated administration of anti-microbial medications.

Median neutrophil counts at the end of each cycle (last value obtained for each patient in each cycle) were lower in the TAS-102 group than in the placebo group, but remained fairly stable through the first six cycles of treatment. Thereafter, the lower numbers of patients remaining on treatment make the data difficult to interpret. The median neutrophil count by cycle at the end of each cycle is summarised below.

Figure 12: RECOURSE; Median neutrophil count by cycle at the end of each cycle, AT population.



Note: The last value recorded in the cycle is selected for inclusion in the display. IQR = interquartile range (Q1 to Q3).

8.4.1.3. Haemoglobin

Across all cycles, among patients in the TAS-102 group who experienced Grade 3 anaemia (n = 96), the median of the lowest values obtained for each patient was 7.3 g/dL (range: 5.10, 7.96 g/dL).

8.4.1.4. Platelets

Across all cycles, among patients in the TAS-102 group who experienced Grade 4 thrombocytopaenia (n = 3), the median of the lowest values obtained for each patient was 22.0 x 10^9/L (range: 21-24 x 10^9/L).

8.4.1.5. Shifts in CTC Grade from Baseline

Shifts of all grades from baseline in haematology parameters were more frequent in the TAS-102 group than in the placebo group.

Table 58: RECOURSE; Shifts from Baseline of at least 1 CTC Grade for haematology parameters of interest, AT population maximum CTC Grade all cycles

Parameter Treatment Group	N [a]	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Leukopaenia					
TAS-102	528	113 (21.4)	181 (34.3)	98 (18.6)	15 (2.8)

Placebo	263	12 (4.6)	0	0	0
Neutropaenia					
TAS-102	528	36 (6.8)	117 (22.2)	140 (26.5)	60 (11.4)
Placebo	263	1 (0.4)	1 (0.4)	0	0
Lymphocytopaenia					
TAS-102	522	101 (19.3)	131 (25.1)	95 (18.2)	17 (3.3)
Placebo	262	38 (14.5)	42 (16.0)	24 (9.2)	2 (0.8)
Anaemia					
TAS-102	528	124 (23.5)	184 (34.8)	96 (18.2)	---b,c
Placebo	263	45 (17.1)	34 (12.9)	8 (3.0)	--- b
Thrombocytopaenia					
TAS-102	528	157 (29.7)	39 (7.4)	24 (4.5)	3 (0.6)
Placebo	263	19 (7.2)	1 (0.4)	0	1 (0.4)

Denominator for percentages: number of patients with at least one post-baseline measurement during treatment (includes patients with missing baseline). There is no CTC Grade 4 for anaemia based on laboratory data only. One adverse event of Grade 4 anaemia was reported.

8.4.2. Clinical chemistry

8.4.2.1. CTC Grade 3 or 4 abnormalities

With the exception of hyperglycaemia, the incidence of Grade 3 or 4 abnormalities in serum chemistry parameters were similar for the two treatment groups or lower in the TAS-102 group than in the placebo group. Grade 3 elevations in glucose were observed in 32 (6.2%) patients in the TAS-102 group compared to 6 (2.4%) patients in the placebo group. The sponsor stated that this numerical imbalance is most likely due to baseline differences in the incidence of hyperglycaemia between the two treatment groups. Forty-eight (48) patients (48/515, 9.3%) in the TAS-102 group, and 9 patients (9/255, 3.5%) in the placebo group had Grade 2 hyperglycaemia at baseline. Of the 48 patients in the TAS-102 group with Grade 2 hyperglycaemia at baseline, 14 worsened from Grade 2 to Grade 3, 21 remained at Grade 2, and 13 improved to Grade 1 or Grade 0 during the treatment period. Shifts of all grades in serum glucose occurred with similar frequency in the TAS-102 and placebo groups, which suggests that TAS-102 has no clinically significant effect on blood glucose levels, particularly when considering the total time on treatment was nearly 4-fold greater in the TAS-102 group than in the placebo group.

Table 59: RECOURSE; Grade 3 or 4 abnormalities in clinical chemistry parameters that worsened from Baseline, AT population

	TAS-102 (n = 533)			Placebo (n = 265)		
Parameter	**N [a]**	**Grade 3, n (%)**	**Grade 4, n (%)**	**N [a]**	**Grade 3, n (%)**	**Grade 4, n (%)**
Albumin	524	13 (2.5)	0	259	9 (3.5)	0
Alkaline	526	42 (8.0)	0	262	28 (10.7)	0
ALT	526	9 (1.7)	1 (0.2)	263	8 (3.0)	2 (0.8)
AST	524	21 (4.0)	2 (0.4)	262	13 (5.0)	3 (1.1)
Bilirubin	526	39 (7.4)	6 (1.1)	262	23 (8.8)	8 (3.1)
Hypocalcaemia	519	2 (0.4)	2 (0.4)	257	1 (0.4)	0
Creatinine	527	5 (0.9)	0	263	1 (0.4)	1 (0.4)
Hypoglycaemia	515	0	1 (0.2)	255	0	1 (0.4)
Hyperglycaemia	515	32 (6.2)	1 (0.2)	255	6 (2.4)	1 (0.4)
Hypokalaemia	527	14 (2.7)	1 (0.2)	263	3 (1.1)	0

Hyperkalaemia	527	3 (0.6)	1 (0.2)	263	8 (3.0)	0
Hyponatraemia	527	26 (4.9)	0	263	12 (4.6)	3 (1.1)
Hypernatraemia	527	1 (0.2)	0	263	0	0

Denominator for percentages: number of patients with at least one post-baseline measurement during treatment (includes patients with missing baseline).

8.4.2.2. Shifts in CTC Grade from Baseline

Shifts from baseline (all CTC grades) in serum chemistry parameters were generally similar for the 2 treatment groups. Shifts from baseline to Grade 1 or Grade 2 hypocalcaemia were more frequent in the TAS-102 group (n = 154, 29.7%) than in the placebo group (n = 50, 19.5%). Shifts from Baseline to Grade 1, 2, 3 or 4 hyperglycaemia occurred with similar frequency in the TAS-102 group (n = 272, 52.8%) as in the placebo group (n = 128, 50.2%). Shifts from Baseline to Grade 1, 2, 3 or 4 hypokalaemia were observed approximately twice as frequently in the TAS-102 group (n = 80, 15.2%) as in the placebo group (n = 19, 7.2%), and 15 (2.8%) patients experienced Grade 3 or 4 hypokalaemia in the TAS-102 group versus 3 (1.1%) patients in the placebo group. The sponsor identified an association between AEs of diarrhoea and vomiting and Grade 3 or 4 hypokalaemia in 6 out of 18 patients (5/15, TAS-102; 1/3, placebo). 1 Grade 3 AE of hypokalaemia in the TAS-102 group was associated with an AE of pollakiuria (Grade 1), and one Grade 3 AE of hypokalaemia reported as an SAE was not considered related to treatment but to concomitant diuretic medication.

8.4.2.3. Hepatobiliary laboratory abnormalities

Hepatobiliary laboratory parameters reported during the study were evaluated according to the FDA Guidance for Industry entitled 'Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009)'. The results did not show an association between TAS-102 and drug induced liver injury (DILI). The distribution of laboratory abnormalities and the pattern of liver chemistry abnormalities were similar for the TAS-102 and placebo groups, despite the nearly 4 fold greater total time on treatment for the TAS-102 group compared to the placebo group. Patients meeting FDA laboratory criteria for assessment of potential DILI in the AT population are summarised below.

There were 3 (0.6%) patients in the TAS-102 group and 2 (0.8%) patients in the placebo group with an ALT > 3 x ULN in conjunction with an increased bilirubin (≥ 2 x ULN) and with an alkaline phosphatase (ALP) < 2 x ULN or missing. However, each of the 3 cases in the TAS-102 group meeting the laboratory criteria for Hy's law had reasons other than DILI to account for the hepatic findings (that is, 1 x 'new mild intrahepatic biliary tree dilatation'; 1 x baseline liver metastases; 1 x bile duct stenosis).

Table 60: RECOURSE; Number (%) of patients meeting FDA laboratory criteria for assessment of potential drug induced liver injury; AT population

	TAS-102 (N = 533)	**Placebo (N = 265)**
Elevation of AT and Bilirubin		
>3xULN AT and >1.5xULN Bilirubin	38 (7.1)	26 (9.8)
>3xULN AT and >2xULN Bilirubin	31 (5.8)	24 (9.1)
>3xULN AT and ≥2xULN Bilirubin and Alkaline phosphatase <2xULN or missing	3 (0.6)	2 (0.8)
>3xULN AT and ≥2xULN Bilirubin and Alkaline phosphatase <2xULN	1 (0.2)	0
>3xULN ALT or AST[a]	77 (14.4)	48 (18.1)
>3xULN ALT	38 (7.1)	19 (7.2)

>3xULN AST	68 (12.8)	45 (17.0)
>5xULN ALT or AST[a]	28 (5.3)	21 (7.9)
>5xULN ALT	10 (1.9)	10 (3.8)
>5xULN AST	24 (4.5)	16 (6.0)
>10xULN ALT or AST[a]	3 (0.6)	7 (2.6)
>10xULN ALT	2 (0.4)	2 (0.8)
>10xULN AST	3 (0.6)	7 (2.6)
>20xULN ALT or AST[a]	2 (0.4)	3 (1.1)
>20xULN ALT	1 (0.2)	2 (0.8)
>20xULN AST	2 (0.4)	3 (1.1)
Elevation of Bilirubin		
>1.5xULN	109 (20.5)	48 (18.1)
>2xULN	71 (13.3)	40 (15.1)
>1.5xULN Alkaline Phosphatase	293 (55.0)	147 (55.5)

AT = aminotransferase; ULN = upper limit of normal range; a. Patients with both ALT and AST abnormalities for the same lab draw (same date and time) are counted as one event.

8.4.2.4. Renal-related laboratory abnormalities

There was no difference between the two treatment groups with respect to the incidence of serum creatinine abnormalities of potential clinical relevance (see below).

Table 61: RECOURSE; Serum creatinine elevations of potential clinical relevance.

Elevation of Serum Creatinine	Number (%) of Patients	
	TAS-102 (N = 533)	Placebo (N = 265)
Change from Baseline ≥ 0.5 mg/dL	24 (4.5)	15 (5.7)
> 1.5xULN Creatinine	24 (4.5)	9 (3.4)
Either Change from Baseline ≥0.5 mg/dL or >1.5xULN Creatinine	30 (5.6)	15 (5.7)
Both Change from Baseline ≥0.5 mg/dL and >1.5xULN Creatinine	18 (3.4)	9 (3.4)

8.5. Vital signs and Electrocardiograph

8.5.1. Vital signs

No clinically relevant mean or median changes in body weight or vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate) were observed in either treatment group during the study. The mean ± SD change in body weight from Baseline to the last collection cycle was -1.33 ± 3.34 kg in the TAS-102 group and -1.2 ± 3.28 kg. The mean ± SD change in systolic blood pressure from baseline to last collection cycle was -3.3 ± 17.04 mmHg in the TAS-102 group and -3.4 ± 16.03 in the placebo group. The mean ± SD change in diastolic blood pressure from Baseline to last collection cycle was -2.5 ± 11.73 mmHg in the TAS-102 group and -1.3 ± 10.76 in the placebo group. The mean ± SD change in heart rate from Baseline to last collection cycle was 2.2 ± 14.59 beats per minute in the TAS-102 group and 2.8 ± 13.44 in the placebo group. The mean ± SD change in respiratory rate from Baseline to last collection cycle was 0.4 ± 3.17 breaths per minute in the TAS-102 group and 0.2 ± 3.37 in the placebo group.

8.5.2. Electrocardiograph

No clinically relevant changes from baseline or differences between treatment groups were observed for standard 12-lead ECG parameters (uncorrected QT, QTcF, QTcB, and ventricular rate) obtained at Baseline (within 28 days prior to Day 1 of Cycle 1), at 2 hours after the first dose of study drug on Day 1 of Cycle 1, at 2 hours after the morning dose of study drug on Day 12 of Cycle 1, or at the End of Treatment visit. No marked differences between the 2 treatment groups were observed for the percentage of patients with categorical values and change from baseline values in QTcF and QTcB at any time point or at each patient's maximum post-baseline value.

8.6. Safety in special groups

8.6.1. Age

The high-level summary of AEs based on age is presented below. In the TAS-102 group, the incidence of each high-level AE category was greater in patients aged ≥ 65 years compared to < 65 years. The categories with ≥ 5% more patients aged ≥ 65 years compared to patients age < 65 years in the TAS-102 group were any ≥ Grade 3 AE and any treatment-related ≥ Grade 3 AE.

Table 62: RECOURSE; Overview of adverse events by age group, AT population

	TAS-102 (N = 533)		Placebo (N = 265)	
	< 65 year (N = 299)	≥65 years (N = 234)	< 65 years (N = 147)	≥65 years (N = 118)
Any adverse event (AE)	293 (98.0)	231 (98.7)	137 (93.2)	110 (93.2)
Any treatment related AE	250 (83.6)	207 (88.5)	82 (55.8)	63 (53.4)
Any ≥ Grade 3 AE	195 (65.2)	175 (74.8)	73 (49.7)	64 (54.2)
Any treatment-related ≥ Grade 3 AE	120 (40.1)	141 (60.3)	16 (10.9)	10 (8.5)
Any serious AE (SAE)	86 (28.8)	72 (30.8)	46 (31.3)	43 (36.4)
Any treatment-related SAE	22 (7.4)	28 (12.0)	0	1 (0.8)

In the TAS-102 group, patients who were aged ≥ 65 years had a higher incidence (difference of at least 5%) compared to those aged < 65 years for AEs of anaemia (50.4% versus 32.1%), neutropaenia (32.9% versus 26.4%), neutrophil count decreased (31.2% versus 25.1%), platelet count decreased (21.4% versus 10.4%), white blood cell count decreased (31.6% versus 24.1%) and decreased appetite (41.9% versus 36.8%). The corresponding incidence of these AEs in the placebo group (≥ 65 years versus < 65 years) were anaemia (9.3% versus 7.5%), neutropaenia (0% versus 0%), neutrophil count decreased (0% versus 0.7%), platelet count decreased (2.5% versus 2.0%), white blood cell count decreased (0% versus 0.7%), decreased appetite (26.3% versus 32.0%). Patients aged < 65 years in the TAS-102 group had a higher incidence of nausea than those aged ≥ 65 years (52.2% versus 43.6%), with a similar trend observed in the placebo group (27.2% versus 19.5%).

Based on clinical laboratory assessments, patients aged ≥ 65 years in the TAS-102 group had a higher incidence (difference of at least 5%) of Grade 3 or 4 leukopaenia (25.5% versus 18.2%), Grade 3 or 4 neutropaenia (47.6% versus 30.3%), Grade 3 anaemia (26.0% versus 12.1%) and Grade 3 or 4 thrombocytopaenia (8.7% versus 2.4%) than patients aged < 65 years. The corresponding incidence of these abnormalities in the placebo group (≥ 65 years versus < 65 years) were Grade 3 or 4 leukopaenia (0% versus 0%), Grade 3 or 4 neutropaenia (0% versus 0%), Grade 3 anaemia (1.7% versus 4.1%) and Grade 3 or 4 thrombocytopaenia (0% versus 0.7%). There were no notable differences between the age subgroups in the incidence of Grade 3 or 4 serum chemistry abnormalities.

Comment: The sponsor's D120 response to the CHMP included a comparison of the AE profile based on age groups of < 65, 65-74, 75-84 and 85+ years in the integrated Groups 1 and 2 safety data sets. There was only 1 patient aged 85+ years in total population included in the two integrated safety data sets. Review of the AE profiles of patients in the TAS-102 treatment group in Group 1 showed no marked differences between patients aged 65-74 years and 75-84 years, with a similar pattern being observed in Group 2. In addition, in the TAS-102 group there were no marked differences in the AE profiles of patients aged < 65 year compared to patients aged ≥ 65 years in either Group 1 or Group 2.

8.6.2. Gender

The high level summary of AEs based on gender is presented below. In the TAS-102 group, the patient incidence in females was ≥ 5% compared to males for any ≥ Grade 3 AE, any treatment-related ≥ Grade 3 AE, and any serious SAE.

Table 63: RECOURSE; Overview of adverse events by gender group, AT population

	TAS-102 (N = 533)		Placebo (N = 265)	
	Male (N = 326)	Female (N = 207)	Male (N = 164)	Female (N = 101)
Any adverse event (AE)	322 (98.8)	202 (97.6)	152 (92.7)	95 (94.1)
Any treatment-related AE	280 (85.9)	177 (85.5)	87 (53.0)	58 (57.4)
Any ≥ Grade 3 AE	213 (65.3)	157 (75.8)	85 (51.8)	52 (51.5)
Any treatment-related ≥ Grade 3 AE	151 (46.3)	110 (53.1)	17 (10.4)	9 (8.9)
Any serious AE (SAE)	89 (27.3)	69 (33.3)	60 (36.6)	29 (28.7)
Any treatment-related SAE	28 (8.6)	22 (10.6)	1 (0.6)	0

In the TAS-102 group, females had a higher incidence (difference of at least 5%) compared to male patients for AEs of anaemia (44.9% versus 37.1%), abdominal pain (18.4% versus 12.6%), abdominal pain upper (12.1% versus 4.0%), diarrhoea (37.2% versus 28.5%), nausea (55.1% versus 44.2%), vomiting (42.0% versus 18.7%), back pain (11.6% versus 5.5%), and cough (14.0% versus 8.6%). The corresponding incidence of these AEs in the placebo group (females versus males) were anaemia (11.9% versus 6.1%), abdominal pain (13.9% versus 13.4%), abdominal pain upper (5.0% versus 4.3%), diarrhoea (13.9% versus 11.6%), nausea (31.7% versus 18.9%), vomiting (19.8% versus 11.0%), back pain (9.9% versus 4.9%), and cough (13.9% versus 9.8%).

Based on clinical laboratory assessments, female patients who received TAS-102 had a higher incidence (difference of at least 5%) of Grade 3 or 4 leukopaenia (24.6% versus 19.4%), Grade 3 or 4 neutropaenia (42.9% versus 34.8%), Grade 3 or 4 lymphocytopaenia (24.9% versus 19.3%) and Grade 3 anaemia (23.2% versus 15.1%) than male patients, with a similar incidence of Grade 3 or 4 thrombocytopaenia (4.4% versus 5.5%). The corresponding incidence of these abnormalities in the placebo group (females versus males) were Grade 3 or 4 leukopaenia (0% versus 0%), Grade 3 or 4 neutropaenia (0% versus 0%), Grade 3 or 4 lymphocytopaenia (4.0% versus 13.5%), Grade 3 anaemia (4.0% versus 2.4%) and Grade 3 or 4 thrombocytopaenia (1.0% versus 0%). There were no notable differences between males and females in the incidence of Grade 3 or 4 serum chemistry abnormalities.

8.6.3. Race and geographic region

In the TAS-102 group, there were 305 White patients, 184 Asian patients, and 4 Black/African American patients. The number of Black/African American patients is too small to make meaningful safety comparisons to the other two racial groups. In the TAS-102 group, 97.7%

(298/305) White patients had an AE (any) compared to 99.5% (183/184) Asian patients, with corresponding incidence in patients in the placebo group being 93.5% (144/154) and 92.6% (87/94), respectively. The AE profiles in White (racial group) and Western (geographical region) patients were similar as were the AE profiles in Asian (racial group) and Asian (geographical region) patients. The CSR included a more detailed summary of patients in the Western and Asian geographical regions. Consequently, the safety data based on geographic regions rather than racial group are discussed below.

There was no consistent pattern in the high-level AE profiles between Western and Asian regions in patients in the TAS-102 group. However, in general the differences in incidence between Western and Asian regions for high-level AE categories were more marked in patients in the TAS-102 group than in the placebo group. The high-level overview of AEs by geographic region are summarised below.

Table 64: RECOURSE; Overview of adverse events by geographic region, AT population

	TAS-102 (N = 533)		Placebo (N = 265)	
	Western (N = 355)	Asia (N = 178)	Western (N = 177)	Asia (N = 88)
Any adverse event (AE)	347 (97.7)	177 (99.4)	166 (93.8)	81 (92.0)
Any treatment-related AE	289 (81.4)	168 (94.4)	92 (52.0)	53 (60.2)
Any ≥Grade 3 AE	252 (71.0)	118 (66.3)	93 (52.5)	44 (50.0)
Any treatment-related ≥Grade 3 AE	163 (45.9)	98 (55.1)	17 (9.6)	9 (10.2)
Any serious AE (SAE)	111 (31.3)	47 (26.4)	55 (31.1)	34 (38.6)
Any treatment-related SAE	29 (8.2)	21 (11.8)	1 (0.6)	0

There were a number of differences between the Western and Asian regions in the incidence of specific AE terms relating to laboratory abnormalities, particularly haematologic abnormalities. The sponsor states that this was due to regional differences in the selection of terms used to describe these abnormalities. For example, in the TAS-102 group, patients enrolled at sites in Asia had a higher incidence of AE preferred term of 'neutrophil count decreased' compared to patients enrolled at Western sites (62.9% versus 10.1%), whereas patients enrolled at Western sites had a higher incidence of AE preferred term of 'neutropaenia' compared to patients at Asian sites (42.8% versus 2.2%).

The marked differences between the two geographic regions in patients with haematologic AEs based on preferred terms was not observed based on Grade 3 or 4 haematologic AEs based on clinical laboratory assessments (that is, same criteria applied to all patients). Based on clinical laboratory assessments, patients enrolled at sites in Asia who received TAS-102, had a higher incidence (difference of at least 5%) of Grade 3 or 4 lymphocytopaenia (26.4% versus 18.9%) and Grade 3 anaemia than patients enrolled at Western sites (23.0% versus 15.7%), with a similar incidence of Grade 3 or 4 leukopaenia (24.2% versus 20.0%), Grade 3 or 4 neutropaenia (37.6% versus 38.0%) and Grade 3 or 4 thrombocytopaenia (6.2% versus 4.6%). The corresponding incidence of these abnormalities in the placebo group (Asian versus Western) was as follows: Grade 3 or 4 leukopaenia (0% versus 0%), Grade 3 or 4 neutropaenia (0% versus 0%), Grade 3 or 4 lymphocytopaenia (12.5% versus 8.6%), Grade 3 anaemia (3.4% versus 2.9%) and Grade 3 or 4 thrombocytopaenia (1.1% versus 0%). There were no notable differences between patients

enrolled in Asia and in the Western region in the incidence of Grade 3 or 4 serum chemistry abnormalities,

In the TAS-102 group, Asian patients had a higher incidence (difference of at least 5%) compared to Western patients for AEs (PTs) of anaemia (51.7% versus 34.4%), abdominal distension (7.9% versus 2.5%), nausea (54.5% versus 45.4%), stomatitis (13.5% versus 5.1%), fatigue (41.6% versus 32.1%), malaise (10.1% versus 1.4%), pyrexia (23.0% versus 16.1%), upper respiratory tract infection (7.9% versus 0.8%), blood bilirubin increased (12.9% versus 6.2%), C-reactive protein increased (7.9% versus 0.6%), neutrophil count decreased (62.9% versus 10.1%), platelet count decreased (33.7% versus 5.9%), WBC count decreased (65.2% versus 8.5%), decreased appetite (53.4% versus 31.8%), and pruritus (7.9% versus 2.5%) The corresponding incidence of these AEs in the placebo group (Asian versus Western) was as follows: anaemia (11.9% versus 9.1%), abdominal distension (8.0% versus 3.4%), nausea (27.3% versus 22.0%), stomatitis (9.1% versus 4.5%), fatigue (18.2% versus 26.0%), malaise (6.8% versus 0%), pyrexia (14.8% versus 13.6%), upper respiratory tract infection (2.3% versus 1.1%), blood bilirubin increased (4.5% versus 9.0%), neutrophil count decreased (1.1% versus 0%), platelet count decreased (2.3% versus 2.3%), WBC count decreased (1.1% versus 0%), decreased appetite (37.5% versus 25.4%), and pruritus (9.1% versus 2.8%).

In the TAS-102 group, Western patients had a higher incidence (difference of at least 5%) compared to Asian patients for AEs (PTs) of neutropaenia (42.8% versus 2.2%), leukopaenia (7.6% versus 1.1%), thrombocytopaenia (10.4% versus 0%), abdominal pain (17.7% versus 9.0%), asthenia (27.3% versus 0%), mucosal inflammation (8.2% versus 0.6%), hypokalaemia (5.1% versus 1.1%), back pain (10.1% versus 3.4%), and dyspnoea (14.1% versus 3.4%). The corresponding incidence of these AEs in the placebo group (Western versus Asian) was as follows: neutropaenia (0% versus 0%), leukopaenia (0% versus 0%), thrombocytopaenia (0% versus 1.1%), abdominal pain (15.8% versus 9.1%), asthenia (16.9% versus 0%), mucosal inflammation (6.2% versus 1.1%), hypokalaemia (2.8% versus 0%), back pain (7.3% versus 5.7%), and dyspnoea (15.3% versus 8.0%).

Comment: The sponsor commented that '(t)he observed differences between Western and Asian patients (in the incidence of AEs) showed similar trends in both treatment groups (TAS-102 and placebo), indicating slight differences for the two regions in AE reporting patterns. Those differences reflect subtle regional differences in the usage of terms (e.g., asthenia versus fatigue) as well as probably cultural differences that influence how patients report events'. The reasons for the difference in the incidence of AEs between the two geographic regions postulated by the sponsor are not unreasonable.

8.6.4. Baseline renal function

The high level AEs based on renal function are summarised below. In patients in the TAS-102 group, there was no marked difference between the normal renal function and mild renal impairment subgroups (based on baseline CLcr) with respect to overall incidence of AEs, ≥ Grade 3 AEs, or serious AEs. However, patients with moderate renal impairment had a higher incidence (difference of at least 5%) of ≥ Grade 3 AEs and serious AEs compared to the other 2 subgroups. In patients in the placebo group, there were no consistent differences in the high level AE profiles across the three subgroups. In patients receiving TAS-102, the incidence of dose reductions in the normal, mild and moderate renal impairment groups based on baseline CLcr was 10.8%, 16.3% and 23.4%, respectively.

Table 65: RECOURSE; Overview of high level AEs by baseline renal function (CLcr), AT population

	Number (%) of Patients					
	TAS-102 (N=533)			Placebo (N=265)		
	Normal (CLcr ≥90 mL/min) (N=306)	Mild Impairment (CLcr 60-89 mL/min) (N=178)	Moderate Impairment (CLcr 30-59 mL/min) (N=47)	Normal (CLcr ≥90 mL/min) (N=145)	Mild Impairment (CLcr 60-89 mL/min) (N=91)	Moderate Impairment (CLcr 30-59 mL/min) (N=26)
Any adverse event (AE)	299 (97.7)	177 (99.4)	46 (97.9)	133 (91.7)	87 (95.6)	24 (92.3)
Any treatment-related AE	258 (84.3)	157 (88.2)	40 (85.1)	82 (56.6)	47 (51.6)	14 (53.8)
Any ≥Grade 3 AE	204 (66.7)	126 (70.8)	40 (85.1)	75 (51.7)	47 (51.6)	14 (53.8)
Any treatment-related ≥Grade 3 AE	138 (45.1)	94 (52.8)	29 (61.7)	17 (11.7)	7 (7.7)	2 (7.7)
Any serious AE (SAE)	84 (27.5)	54 (30.3)	20 (42.6)	44 (30.3)	36 (39.6)	8 (30.8)
Any treatment-related SAE	28 (9.2)	16 (9.0)	6 (12.8)	1 (0.7)	0	0

In the TAS-102 group, the incidence of the most frequently reported AEs in patients in the normal renal function group (≥ 10%) compared to the incidence in patients in the mild and moderate renal impairment groups were, respectively, nausea (52.3% versus 44.4% versus 36.2%), decreased appetite (36.9% versus 41.6% versus 40.4%), fatigue (35.6% versus 32.0% versus 42.6%), anaemia (33.7% versus 45.5% versus 61.7%), diarrhoea (30.4% versus 33.1% versus 38.3%), neutropaenia (29.7% versus 28.1% versus 31.9%), vomiting (27.1% versus 29.2% versus 25.5%), neutrophil count decreased (23.5% versus 35.4% versus 27.7%), white blood cell count decreased (22.9% versus 32.6% versus 38.3%), asthenia (19.3% versus 17.4% versus 14.9%), pyrexia (17.6% versus 18.5% versus 21.3%), constipation (16.0% versus 14.0% versus 12.8%), abdominal pain (15.0% versus 13.5% versus 19.1%), platelet count decreased (13.1% versus 15.2% versus 27.7%), cough (12.1% versus 10.7% versus 2.1%), dyspnoea (11.8% versus 9.0% versus 8.5%), and peripheral oedema (10.1% versus 9.6% versus 10.6%). Overall, there was no consistent relationship across the normal renal function, mild renal impairment and moderate renal impairment groups as regards the patient incidence of those AEs most frequently (≥ 10%) reported in the normal renal function group.

8.6.5. ECOG PS (0 versus 1)

The high level summary of AEs based on ECOG PS (0 versus 1) is presented below. In the TAS-102 group, any ≥ Grade 3 AE and any SAE were reported in ≥ 5% more patients in the PS=1 subgroup than in the PS=0 subgroup. However, the differences between the two subgroups were not consistent.

Table 66: RECOURSE; Overview of high level AEs by baseline ECOG (PS = 0, PS = 1), AT population.

	TAS-102 (N = 533)		Placebo (N = 265)	
	PS=0 (N = 301)	PS=1 (N = 232)	PS=0 (N = 147)	PS=1 (N = 118)
Any adverse event (AE)	295 (98.0)	229 (98.7)	132 (89.8)	115 (97.5)
Any treatment-related AE	264 (87.7)	193 (83.2)	81 (55.1)	64 (54.2)
Any ≥Grade 3 AE	201 (66.8)	169 (72.8)	59 (40.1)	78 (66.1)
Any treatment-related ≥Grade 3 AE	153 (50.8)	108 (46.6)	12 (8.2)	14 (11.9)
Any serious AE (SAE)	77 (25.6)	81 (34.9)	35 (23.8)	54 (45.8)
Any treatment-related SAE	22 (7.3)	28 (12.1)	1 (0.7)	0

In the TAS-102 group, patients with PS=1 had a higher incidence (difference of at least 5%) compared to those with PS=0 at baseline for AE of vomiting (31.9% versus 24.6%). A similar difference between the two PS subgroups in the incidence of vomiting was observed in the placebo group (22.9% (PS = 1) versus 7.5% (PS = 0)). However, patients with PS = 0 had a higher incidence (difference of at least 5%) compared to those with PS = 1 for AEs of diarrhoea (35.2% versus 27.6%), fatigue (39.5% versus 29.7%), neutrophil count decreased (33.2% versus 20.7%), platelet count decreased (18.9% versus 10.3%), and white blood cell count decreased (33.2% versus 19.8%). The corresponding incidences of these AEs in the placebo group (PS = 0 versus PS = 1) were diarrhoea (7.5% versus 18.6%), fatigue (21.8% versus 25.4%), neutrophil count decreased (0.7% versus 0%), platelet count decreased (2.7% versus 1.7%), and white blood cell count decreased (0.7% versus 0%).

8.7. Post-marketing experience

The first country in which trifluridine/tipiracil (Lonsurf) was approved for marketing was Japan. The medicine was approved in Japan on 24 March 2014 and launched for marketing on 26 May 2015. The approved indication in Japan was amended on 20 March 2015 to include 'unresectable advanced or recurrent colorectal cancer', based on the results of RECOURSE. The sponsor estimates that cumulative exposure in Japan from May 2014 to June 2015 is approximately 7037 patients.

There have been 205 serious adverse reactions (SARs) in 110 cases from Japanese post-marketing experience reported from 25 July 2014 until 24 July 2015. Of the 205 reported SARs, 39 events in 22 case reports were characterised as suspected unexpected serious adverse reactions (SUSARs). The 39 SUSAR events included 6 events of 'Febrile neutropaenia', 5 events of 'Disseminated intravascular coagulation', 4 events of 'Interstitial lung disease', 2 events of 'Pneumonia', 2 events of 'Bone marrow failure', 2 events of 'Cardiac failure congestive', and 1 event each of 'Anaemia', 'Pancytopaenia', 'Atrial fibrillation', 'Atrial flutter', 'Left ventricular dysfunction', 'Corneal disorder', 'Small intestinal perforation', 'Pyrexia', 'Jaundice', 'Infection', 'Infected fistula', 'Platelet count decreased', 'White blood cell count decreased', 'Hypocalcaemia', 'Hypomagnesaemia', 'Cerebral infarction', 'Acute respiratory distress syndrome', and 'Pulmonary haemorrhage'.

Of the 5 cases of 'Disseminated intravascular coagulation' reported during the collection period, 4 were considered to be possibly related to Lonsurf since these events were probably secondary to infection caused by chemotherapy induced bone-marrow suppression which increases susceptibility to infection. The remaining case was assessed as 'Unassessable' at the time of data lock point for the following reasons. In this case, no infection was diagnosed, and 'DIC' was reportedly due to oncolysis. Necrosis within multiple lung metastases and retroperitoneal lymph nodes was observed.

In a document titled 'Post-marketing experience in patients with unresectable advanced or recurrent colorectal cancer' provided the sponsor stated that '(T)o date, TAS-102 has been authorised for use in two countries, Japan (March 24, 2014) and USA (September 22, 2015). There have been reports of interstitial lung disease in patients receiving Lonsurf in post-approval use in Japan'.

8.8. Other safety issues

8.8.1. Updated safety information from the clinical development program

As of 24 July 2015, a cumulative total of 2212 patients have been treated in the TAS-102 clinical development program globally (completed and ongoing clinical trials). Of the 2212 patients, 1448 patients received TAS-102 alone, 27 patients received TAS-102 plus irinotecan, 406 patients received 'blinded' TAS-102, 9 patients received comparators, and 322 patients received placebo.

Since the inception of the clinical program through to 24 July 2015, a total of 572 patients have experienced SAEs, with the majority being 'gastrointestinal disorders', and a total of 131 patients

have experienced SARs, with the majority being 'blood and lymphatic system disorders'. The safety profile of TAS-102 is based on patients from the EU, Asia, Japan, Australia and the US.

Important identified risks associated with TAS-102 include bone marrow suppression (anaemia, neutropaenia, leukopaenia, thrombocytopaenia, and febrile neutropaenia), gastrointestinal events (nausea, vomiting and diarrhoea) and infections. Important potential risks which have been identified include use of TAS-102 in patients with moderate renal impairment, and use in pregnant or breast-feeding women.

8.8.2. Drug-drug interactions

No clinical drug-drug interaction studies involving TAS-102 have been performed.

8.8.3. Use in pregnancy and lactation

It is not known whether TAS-102 or its metabolites are excreted in human milk.

8.8.4. Hospitalisations

The submission included a 'Hospitalisation Analysis', which evaluated the hospitalisation data reported during the pivotal Phase III study (RECOURSE). Of the 800 randomised patients, 798 were treated (AT population) and included in the hospitalisation analysis. Overall, no evidence of increased risk of hospitalisation in patients in the TAS-102 group compared to the placebo group was observed in the hospital analysis.

The median number of days hospitalised and median hospitalisation ratio (days hospitalised divided by days of follow-up) were lower for the TAS-102 group (9.00 days, 0.12) than for the placebo group (11.00 days, 0.22). The ratio of hospitalisations per patient was lower for the TAS-102 group (206/533, 0.39) than for the placebo group (121/265, 0.46). The percentage of patients hospitalised was also lower for the TAS-102 group (31.0% of patients) than for the placebo group (36.2% of patients). SAEs were the primary reason for hospitalisations per patient: 183/533 (34.3%) and 101/265 (38.1%) in the TAS-102 and placebo groups, respectively. Of these hospitalisations, 25/533 (4.7%) in the TAS-102 group and 15/265 (5.7%) in the placebo group included an additional reason for hospitalisation. Hospitalisations during the treatment period and/or 30 day follow-up are summarised below.

Hospitalisations for febrile neutropaenia during the treatment period and/or 30 day safety follow up period were analysed. There were no patients hospitalised for febrile neutropaenia in the placebo group. In the TAS-102 group, all 14 patients hospitalised for febrile neutropaenia were due to SAE without an additional reason; the median number of days hospitalised was 9.50 days, and the median hospitalisation ratio was 0.16.

The percentage of SAEs resulting in hospitalisation was lower in the TAS-102 group (28.3% of patients) than in the placebo group (32.5% of patients). SAEs reported in ≥ 1% of patients in either treatment group and occurring more frequently in the TAS-102 group than in the placebo group, respectively, were febrile neutropaenia (2.6% (n = 14) versus 0% (n = 0)), anaemia (2.1% (n = 11) versus 0% (n = 0)), and vomiting (1.1% (n = 6) versus 0% (n = 0)). SAEs reported in ≥ 1% of patients in either treatment group and occurring more frequently in the placebo group than in the TAS-102 group, respectively, were general health deterioration (3.4% (n = 9) versus 2.8% (n = 15)), dyspnoea (2.3% (n = 6) versus 0.6% (n = 3)), decreased appetite (1.9% (n = 5) versus 0.6% (n = 3)), abdominal pain (1.5% (n = 8) versus 1.9% (n = 5)), hepatic failure (1.5% (n = 4) versus 0% (n = 0)), urinary tract infection (1.1% (n = 3) versus 0.4% (n = 2)), and tumour pain (1.1% (n = 3) versus 0.4% (n = 2)).

Table 67: RECOURSE; Hospitalisations during treatment and/or safety follow-up, AT population

	TAS-102 (N=533)				Placebo (N=265)			
Reason(s) Hospitalised	Events n	Patients n (%)	Median Total Days Hospitalised[a]	Median Hospitalisation Ratio[b]	Events n	Patients n (%)	Median Total Days Hospitalised[a]	Median Hospitalisation Ratio[b]
All Reasons	206	165 (31.0)	9.00	0.12	121	96 (36.2)	11.00	0.22
SAE	183	151 (28.3)	9.00	0.12	101	86 (32.5)	11.00	0.23
SAE Alone	158	131 (24.6)	9.00	0.12	86	74 (27.9)	11.00	0.21
SAE & Elective Preplanned Surgery	2	2 (0.4)	7.00	0.09	1	1 (0.4)	4.00	0.03
SAE & Hospice/Palliative Care	13	11 (2.1)	14.00	0.20	13	13 (4.93)	12.00	0.23
SAE & Palliative Radiation	0	0	0	0	1	1 (0.4)	10.00	0.10
SAE and Other	10	10 (1.9)	5.50	0.04	0	0	0	0
Elective Preplanned Surgery Alone	4	4 (0.8)	3.00	0.04	0	0	0	0
Hospice/Palliative Care Alone	4	4 (0.8)	7.50	0.12	9	8 (3.0)	8.00	0.14
Palliative Radiation Alone	1	1 (0.2)	11.00	0.08	2	1 (0.4)	13.00	0.31
Other Alone	14	14 (2.6)	5.00	0.04	9	8 (3.0)	2.00	0.04

a. For each patient, if applicable the total number of days hospitalised is summed across multiple events by reason (that is, by reason displayed in the rows of the table) prior to calculation of the median; b. For each patient the hospitalisation ratio is calculated according to reason as the total days hospitalised divided by the total days followed. Total days followed for each patient = maximum (last dose of study medication +30, last hospitalisation discharge date) or the date of death, whichever comes first, minus first dose date +1.

8.8.5. Drug abuse

Not applicable.

8.8.6. Withdrawal and rebound

Not applicable.

8.8.7. Effects on ability to drive or operate machinery or impairment of mental ability

AEs in the integrated safety data Groups 1 and 2 likely to adversely affect the ability to drive or operate machinery or impair mental ability are summarised. AEs of interest (all grades) reported in ≥ 1% of patients in either of the two treatment groups and more frequently in the TAS-102 group than in the placebo group in both Groups 1 and 2 were asthenia and fatigue. Other relevant AEs were reported with similar frequencies in both treatment groups.

8.9. Evaluator's overall conclusions on clinical safety

The safety of TAS-102 for the proposed indication has been satisfactorily characterised in the pivotal Phase III study (RECOURSE). The most frequently reported toxicities observed with TAS-102 were associated with myelosuppression (anaemia, leukopaenia, neutropaenia, febrile neutropaenia and thrombocytopaenia), gastrointestinal events (nausea, vomiting and diarrhoea), and infections (predominantly nasopharyngitis, urinary tract infection, and upper respiratory tract infection). The toxicities associated with TAS-102 were generally manageable by reductions in dose, interruptions in dose and delays in cycle initiation, rather than dose discontinuation.

In RECOURSE, the safety population included 533 patients with mCRC who had been treated with TAS-102 (mean of 12.7 and median of 6.7 weeks of exposure) and 265 patients in the placebo group (mean of 6.8 and median of 5.7 weeks of exposure). The mean ± SD (and median) number of 28 day treatment cycles initiated in the two treatment groups was 3.4 ± 2.56 (median 2.0) in the TAS-102 group and 2.3 ± 1.49 (median 2.0) in the placebo group. There are limited data on patients who have been treated for longer than 6 months, with a maximum of 6 x 28 day treatment cycles being initiated in only 37 (6.9%) patients in the TAS-102 group and 3 (1.1%) of patients in the placebo group. The small number of 28 day cycles initiated in both treatment groups, and the small number of patients for whom a maximum of 6 cycles were initiated reflects the relatively poor prognosis of the patients with refractory mCRC included in the pivotal study.

Overall, the total number of weeks of exposure in RECOURSE was approximately 4 fold longer in the TAS-102 group than in the placebo group (6743 versus 1791 weeks respectively). The notably longer period of exposure in the TAS-102 group compared to the placebo group should be taken into account when comparing the AE data between the two treatment groups. No safety data could be identified in the study report comparing safety outcomes in the two treatment groups adjusted for duration of exposure.

In RECOURSE, nearly all patients in both treatment groups experienced at least 1 AE (98.3%, TAS-102; 93.2%, placebo), and the majority of AEs in both treatment groups were considered by investigators to be treatment-related (85.7%, TAS-102; 54.7%, placebo). AEs categorised as Grade ≥ 3 in severity were reported more frequently in patients in the TAS-102 group than in the placebo group (69.4% versus 51.7%), as were treatment related Grade ≥ 3 AEs (49.0% versus 9.8%). However, SAEs were reported more frequently in the placebo group than in the TAS-102 group (33.6% versus 29.6%), as were AEs resulting in death (11.3% versus 3.2%).

In RECOURSE, although nearly all patients in both treatment groups experienced at least 1 AE, the majority of events were manageable by dose modifications rather than treatment discontinuation. AEs resulting in interruption/delay or reduction of study medication were reported in 54.2% of patients in the TAS-102 group and 13.6% of patients in the placebo group, while AEs resulting in treatment discontinuation (including AEs associated with disease progression) were reported in 10.3% of patients in the TAS-102 group and 13.6% of patients in the placebo group. However, adverse events/SAEs were considered to be the primary reason for discontinuation in only 3.6% of patients in the TAS-102 group and 1.5% of patients in the placebo group.

In RECOURSE, there was no evidence that TAS-102 was associated with an increased risk of hepatobiliary related adverse events, but TAS-102 was associated with a small increased risk of renal related adverse events (predominantly proteinuria). Thromboembolic events were reported marginally more frequently in patients in the TAS-102 group compared to placebo, with the difference relating to the increased risk of pulmonary embolism. There was no evidence that TAS-102 was associated with an increased risk of cardiac disorders (ischaemia or arrhythmia). Patients in the TAS-102 group were not and an increased risk of hospitalisation compared to patients in the placebo group.

Haematological laboratory tests (RECOURSE) showed that Grade ≥ 3 abnormalities for leukopaenia, neutropaenia, lymphocytopaenia, anaemia, and thrombocytopaenia were reported more frequently in the TAS-102 group than in the placebo group. Clinical chemistry laboratory tests (RECOURSE) showed that Grade ≥ 3 abnormalities for hyperglycaemia occurred more frequently in patients in the TAS-102 group compared to the placebo groups, with Grade ≥ 3 abnormalities for other clinical chemistry parameters not notably differing between the two treatment groups. Hepatobiliary laboratory abnormalities (AST, ALT, bilirubin, SAP) did not notably differ between the two treatment groups. Hy's law biochemical criteria for drug induced liver injury were reported in 3 patients in the TAS-102 group and 2 patients in the placebo group. However, for each of the 3 patients in the TAS-102 group the biochemical criteria were explained by hepatic conditions other than drug induced hepatic toxicity. Renal laboratory abnormalities associated with serum creatinine concentration did not significantly differ between the two treatment groups. There were no notably differences between the two treatment groups in vital signs or in ECG changes relating to QTc prolongation.

In RECOURSE, the overall safety profile for TAS-102 was inferior in patients aged ≥ 65 years compared to patients aged < 65 years, female patients compared to male patients, and patients with moderate renal impairment compared to patients with normal renal function and patients with mild renal impairment.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of trifluridine/tipiracil (TAS-102), given the proposed usage, are considered to be favourable. In the pivotal Phase III study (RECOURSE), TAS-102 plus BSC significantly prolonged the median time to OS by 1.8 months compared to placebo plus BSC (primary efficacy endpoint). In the TAS-102 group, the median OS was 7.1 months compared to 5.3 months in the placebo group: HR = 0.68 (95% CI: 0.58, 0.81)); p < 0.0001 (1 sided and 2 sided) stratified log-rank test. The Kaplan-Meier curves began to separate in favour of the TAS-102 group at about 3 months, and remained separated throughout the remainder of the study. The Kaplan-Meier estimates for the percentage of patients surviving at 12 months were 26.6% in the TAS-102 group and 17.6% in the placebo group. The results for the updated OS analysis were consistent with those for the primary analysis.

In addition, the median OS was consistently longer in the TAS-102 group compared with the placebo group across all three stratification analyses (that is, KRAS status (wild versus mutant type); time since diagnosis of first metastasis (< 18 months versus ≥ 18 months); region (Asia versus Western)). Furthermore, pre-specified analyses of OS in various subgroups (including age, gender and race) consistently favoured longer survival in the TAS-102 group compared to placebo.

The results for PFS (the key secondary efficacy endpoint) from RECOURSE support the OS results. The median PFS, including death due to any cause and progression assessed by investigators using radiologic imaging, was significantly prolonged by 0.3 months in the TAS-102 group compared to the placebo group. In the TAS-102 group, the median PFS was 2.0 months compared to 1.7 months in the placebo group: HR = 0.48 (95% CI: 0.41, 0.57); p < 0.0001 (1-sided and 2- sided) stratified log-rank test. The Kaplan-Meier estimates for the percentage of patients with PFS at 8 months was 8.0% in the TAS-102 group and 1.4% in the placebo group. In general, the (exploratory) results for the other secondary efficacy endpoints from RECOURSE supported the results for PFS.

There were no data in RECOURSE relating to patient or physician reported life-style outcomes. However, the time to worsening of ECOG PS ≥ 2 was longer in the TAS-102 group compared with to the placebo group (5.7 versus 4.0 months, respectively); which provides some evidence that TAS-102 might have a modest beneficial effect on quality of life.

The modest increases in OS and PFS in the TAS-102 group compared with the placebo group observed in RECOURSE should be interpreted in the context of patients with mCRC who have been heavily pre-treated with standard chemotherapies.

The benefits of TAS-102 on OS and PFS compared to placebo observed in RECOURSE were supported by the results in Japanese patients from Study J003-0040030. In Japanese patients, treatment with TAS-102 significantly increased median OS by 2.4 months and median PFS by 1.0 month compared to placebo. In the TAS-102 group, the median OS was 9.0 months compared to 6.6 months in the placebo group: HR = 0.56 (95% CI: 0.39, 0.81); p = 0.0011, stratified log-rank test. The effect of TAS-102 on OS was consistent across all pre-specified subgroup analyses. The median PFS assessed by independent review committee was 2.0 months in the TAS-102 group compared to 1.0 month in the placebo group: HR=0.41; 95% CI: (0.28, 0.59); p < 0.0001, stratified log-rank test).

9.2. First round assessment of risks

The risks of trifluridine/tipiracil (TAS-102), given the proposed usage, are considered to be favourable. The adverse events associated with TAS-102 are consistent with a medicine containing an antineoplastic thymidine-based nucleoside analogue (that is, trifluridine), which interferes with DNA synthesis and inhibits cell proliferation.

Overall, the safety data from the pivotal Phase III study (RECOURSE) demonstrated that the safety profile of TAS-102 was inferior to the safety profile of placebo. The most frequently reported risks

associated with TAS-102 were myelosuppression (anaemia, leukopaenia, neutropaenia, febrile neutropaenia and thrombocytopaenia), gastrointestinal events (nausea, vomiting and diarrhoea), and infections (predominantly nasopharyngitis, urinary tract infection, and upper respiratory tract infection). In general, the adverse events associated with TAS-102 were manageable by treatment interruption, delays in cycle initiation, and reductions in dose rather that by treatment discontinuation.

The risks of treatment identified with TAS-102 for the proposed usage are based on reporting over a short duration of exposure, with a maximum of 6 x 28 day treatment cycles being initiated in only 37 (6.9%) patients in the TAS-102 group and 3 (1.1%) patients in the placebo group. The short duration of exposure reflects the poor prognosis of patients included in the pivotal study. The total duration of exposure to TAS-102 was approximately 4-fold greater than for placebo (6743 versus 1791 weeks, respectively), and this should be taken into account when comparing the safety profiles of the two treatment groups. The risks of treatment with TAS-102 compared to placebo discussed below relate to the data from the pivotal Phase III study (RECOURSE). The safety results from the pivotal study were consistent with the safety results from the integrated safety data sets (Groups 1 and 2), and with the limited post-marketing safety experience reported in Japanese patients.

9.2.1. Haematologic toxicities

The risk of experiencing a 'blood and lymphatic disorder' (SOC) was 5.2 fold greater for patients in the TAS-102 group compared to patients in the placebo group (57.0% versus 10.9%), while the risk of experiencing a Grade ≥ 3 AE in this SOC was 8.5-fold greater (35.5% versus 4.2%). The higher incidence of AEs in this SOC in the TAS-102 group compared to the placebo group was primarily due to the increased risk of AEs associated with myelosuppression. There were no deaths in either of the two treatment groups reported for haematologic adverse events.

The risks of AEs associated with myelosuppression were markedly greater in the TAS-102 group than in the placebo group. The frequency of preferred term (PT) AEs (any (≥ Grade 3)) associated with myelosuppression reported in patients in the TAS-102 group compared to the placebo group (respectively) were: anaemia (40.2% (16.1%) versus 8.3% (2.6%)); neutropaenia (29.3% (20.1%) versus 0% (0%)); thrombocytopaenia (6.9% (2.1%) versus 0.4% (0.4%)); leukopaenia (5.4% (2.4%) versus 0% (0%)); and febrile neutropaenia (3.8% (3.8%) versus 0% (0%)). There were no fatal AEs (Grade 5) due to anaemia, neutropaenia, leukopaenia, thrombocytopaenia or febrile neutropaenia in either of the 2 treatment groups.

Although haematologic toxicities were reported frequently in patients in the TAS-102 group, discontinuations due to 'blood and lymphatic system disorders' occurred uncommonly (0.6%, TAS-102; 0%, placebo). The only haematologic AEs (PT) in this SOC (TAS-102 versus placebo) resulting in treatment discontinuation were anaemia (0.4% versus 0%), disseminated intravascular coagulation (0.2% versus 0%), and neutropaenia (0.2% versus 0%). In contrast to treatment discontinuations, interruption/delay or reduction of study medication due to 'blood and lymphatic system disorders' occurred frequently in patients in the TAS-102 group and notably more commonly than in the placebo group (26.5% versus 0.8%, respectively). Interruption/delay or reduction of study medication due to haematologic AEs (PT) in this SOC were reported in ≥ 2% of patients in the TAS-102 group (vs placebo) for neutropaenia (19.9% versus 0%), anaemia (5.4% versus 0.8%), and febrile neutropaenia (2.1% versus 0%).

Blood transfusions were received by 16.9% (n = 90) patients in the TAS-102 group and 3.0% (n = 8) of patients in the placebo group. The percentage of patients in the TAS-102 group who received blood transfusions is consistent with the percentage of patients in the group with Grade ≥ 3 anaemia based on haematologic laboratory results. Granulocyte colony stimulating factors (G-CSF) were received by 9.4% (n = 51) of patients in the TAS-102 group as supportive therapy during the study compared to no patients in the placebo group.

9.2.2. Gastrointestinal toxicities

The risk of experiencing 'gastrointestinal disorders' (SOC) was higher in patients in the TAS-102 group compared to the placebo group (77.5% versus 60.8%), while the risk of experiencing Grade ≥ 3 AEs in this SOC was similar in the two treatment groups (12.0% versus 13.6%, respectively). The three most commonly reported gastrointestinal AEs (PT) reported in the TAS-102 (vs placebo) were (any (Grade ≥ 3)): nausea (48.4% (1.9%) versus 23.8% (1.1%)); diarrhoea (31.9% (3.0%) versus 12.5% (0.4%)), and vomiting (27.8% (2.1%) versus 14.3% (0.4%)). Discontinuations due to nausea, vomiting or diarrhoea each occurred in ≤ 2 (≤ 0.4%) patients in the TAS-102 group, and ≤ 1 (0.2%) patients in the placebo group. Interruption/delay or reduction of study medication also occurred relatively infrequently in patients in both the TAS-102 and placebo groups for each of the three commonly reported events: that is, nausea (1.9% versus 0.4%, respectively), vomiting (1.9% versus 0%, respectively), and diarrhoea (2.4% versus 0%). Of note, stomatitis (any grade) was reported in 7.9% of patients in the TAS-102 group and 6.0% of patients in the placebo group, with stomatitis Grade ≥ 3 being reported in 0.4% and 0% of patients, respectively. There were no fatal 'gastrointestinal disorders' in the TAS-102 group, while 5 deaths were reported to be due to 'gastrointestinal disorders' in patients in the placebo group.

9.2.3. Infections and infestations

The risk of experiencing 'infections and infestations' (SOC) was greater in patients in the TAS-102 group compared to the placebo for any events (27.0% versus 15.8%) and Grade ≥ 3 AEs (6.6% versus 4.9%). The most commonly reported AEs (any) occurring in ≥ 1% of patients in the TAS-102 group (vs placebo) were nasopharyngitis (4.3% versus 1.5%), urinary tract infection (3.4% versus 1.9%), URTI (3.2% versus 1.5%), herpes zoster (1.5% versus 0%), bronchitis (1.5% versus 0.8%), and biliary tract infection (1.3% versus 0.4%). Discontinuations due to 'infections and infestations' were reported infrequently in the TAS-102 group compared to the placebo group (0.6% versus 0.8%), with discontinuations in the 3 patients in the TAS-102 group being due to bacterial peritonitis, staphylococcal pneumonia, and sepsis. Interruption/delay or reductions of study medication were reported in 4.7% of patients in the TAS-102 group compared to 2.3% of patients in the placebo group, with the only events reported in ≥ 2 patients in the TAS-102 group (vs placebo) being herpes zoster (4, 0.8% versus 0, 0%), biliary tract infection (2, 0.4% versus 0, 0%), nasopharyngitis (2, 0.4% versus 0, 0%), URTI (2, 0.4% versus 0, 0%), and urinary tract infection (2, 0.4% versus 1, 0.4%).

Fatal AEs due to 'infections and infestations' were reported in 3 (0.6%) patients in the TAS-102, and included 1 event each for liver abscess, staphylococcal pneumonia, sepsis and septic shock. There were no deaths due to 'infections and infestations' reported in patients in the placebo group.

9.2.4. Thromboembolic events (arterial or venous)

Arterial or venous thromboembolic events (all Grades) were reported more frequently in patients in the TAS-102 group than in the placebo group (3.9% versus 2.3%, respectively), and the majority of events in both groups were ≥ Grade 3 in severity (2.1% versus 1.5%, respectively). The major difference between the two treatment groups related to the higher incidence of pulmonary embolism (all Grades) in the TAS-102 group compared to the placebo group (1.7% (n = 9) versus 0% (n = 0)). All pulmonary embolisms in the TAS-102 group were ≥ Grade 3 in severity, and included one fatal case. Despite the higher patient incidence of pulmonary embolism in the TAS-102 group compared to the placebo group, deep venous thrombosis was reported in a similar proportion of patients in both treatment groups (0.6% versus 0.8%, respectively).

9.2.5. Other risks of special clinical interest

Other risks (any AEs (Grade ≥ 3 AEs)) of special clinical interest reported a similar percentage of patients in the TAS-102 and placebo groups, respectively, were: bleeding (8.1% (0.6%) versus 8.7% (3.0%)); 'cardiac disorders', SOC (3.9% (0.8%) versus 4.5% (1.1%)); 'hepatobiliary disorders', SOC (10.3% (6.2%) versus 10.6% (6.8%)); 'neoplasms benign, malignant and unspecified (incl cysts and polyps', SOC (8.6% (0.8%) versus 13.2% (3.4%)); 'nervous system disorders' (21.2% (2.1%) versus 19.6% (4.2%)); 'renal and urinary disorders', SOC (13.1% (2.3%)

versus 11.3% (3.0%)); 'immune system disorders', SOC (0.4% (0%) versus 0.4% (0.4%)), with 1 anaphylactic reaction being reported in the placebo group (none in the TAS-102 group) and 1 hypersensitivity reaction being reported in the TAS-102 group (none in the placebo group).

'Skin and subcutaneous tissue disorders', SOC were reported more frequently in patients in the TAS-102 group compared to the placebo group (23.8% versus 18.1%), with the greatest difference between the two groups being due to increased alopecia in the TAS-102 group compared to the placebo group (6.8% versus 1.1%). Grade ≥ 3 AEs in this SOC were reported infrequently in both treatment groups (0.4%, TAS-102 (1x decubitus ulcer, 1 x urticaria); 0.8%, placebo (1 x pruritus, 1 x rash). There were no reported cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in either treatment group.

9.2.6. Commonly occurring AEs (PT)

At least 1 AE was reported in 98.3% of patients in the TAS-102 group and 93.2% of patients in the placebo group. AEs in the TAS-102 group occurring with a frequency of ≥ 20% (vs placebo) were nausea (48.4% versus 23.8%), anaemia (40.2% versus 8.3%), decreased appetite (39.0% versus 29.4%), fatigue (35.3% versus 23.4%), diarrhoea (31.9% versus 12.5%), neutropaenia (29.3% versus 0%), neutrophil count decreased (27.8% versus 0.4%), vomiting (27.8% versus 14.3%), and WBC decreased (27.4% versus 0.4%).

AEs reported in ≥ 5% of patients in the TAS-102 group, and in ≥ 5% more patients than in the placebo group were nausea (48.4% versus 23.8%), anaemia (40.2% versus 8.3%), decreased appetite (39.0% versus 29.4%), fatigue (35.3% versus 23.4%), diarrhoea (31.9% versus 12.5%), neutropaenia (29.3% versus 0%), neutrophil count decreased (27.8% versus 0.4%), vomiting (27.8% versus 14.3%), WBC decreased (27.4% versus 0.4%), asthenia (18.2% versus 11.3%), platelet cell count decreased (15.2% versus 2.3%), thrombocytopaenia (6.9% versus 0.4%), alopecia (6.8% versus 1.1%), and leukopaenia (5.4% versus 0%).

9.2.7. Commonly occurring Grade 3 or Grade 4 AEs

Grade 3 AEs in the TAS-102 group occurring in ≥ 5% of patients (vs placebo) were anaemia (15.9% versus 2.6%), neutropaenia (13.7% versus 0%), neutrophil count decreased (11.8% versus 0%), and WBC count decreased (9.2% versus 0%). Grade 4 AEs in the TAS-102 group occurring in ≥ 2% of patients were neutropaenia (6.4% versus 0%) and neutrophil count decreased (4.1% versus 0%).

9.2.8. Deaths and other serious adverse events

Deaths reported after the first dose of study medicine and ≤ 30 days after the last dose occurred notably more frequently in the placebo group than in the TAS-102 group (12.4% versus 6.6%). Fatal AEs were reported in 3.2% (n = 17) of patients in the TAS-102 group and 11.3% (n = 30) of patients in the placebo group. The most frequently reported fatal AE in both treatment groups was general physical health deterioration, which was reported in 6 patients (1.1%) in the TAS-102 group, and 8 (3.0%) patients in the placebo group. In the TAS-102 group, 2 patients died due to hepatic failure, and 2 died due to acute renal failure. In the placebo group, 6 patients died due to hepatic failure, 1 died due to renal failure and 1 died due to renal impairment. One (1) patient in the TAS-102 group and 4 patients in the placebo group had fatal AEs of dyspnoea. All other fatal AEs occurred in 1 patient each. The only treatment-related death occurred in 1 patient in the TAS-102 group (Klebsiella pneumonia/septic shock).

SAEs (all grades) were reported in 29.6% of patients in the TAS-102 group and 33.6% of patients in the placebo group, and were predominantly ≥ Grade 3 in severity in both treatment groups (25.9% versus 30.2%, respectively). SAEs (all grades) reported in ≥ 1% of patients in the TAS-102 group (vs placebo) were general physical health deterioration (2.8% versus 4.2%), febrile neutropaenia (2.6% versus 0%), anaemia (1.9% versus 0%), abdominal pain (1.5% versus 1.9%), vomiting (1.3% versus 0%), and pulmonary embolism (1.1% versus 0%).

9.2.9. Discontinuations due to AEs

Discontinuations with the primary reason given as adverse event/SAE were reported in 3.6% (19/533) of patients in the TAS-102 group and 1.5% (4/265) of patients in the placebo group. Adverse events/SAEs identified as the primary reason for discontinuation and reported in ≥ 2 patients (≥ 0.4%) in the TAS-102 group (n = 533) compared to the placebo group (n = 265), were fatigue (0.8% (n = 4) versus 0% (n = 0)), anaemia (0.4% (n = 2) versus 0% (n = 0)), diarrhoea (0.4% (n = 2) versus 0% (n = 0)), ileus (0.4% (n = 2) versus 0% (n = 0)), and general physical health deterioration (n = 2 (0.4% versus n = 1 (0.4%)).

9.2.10. Dose reductions due to AEs

AEs resulting in dose reduction were reported in 13.5% of patients in the TAS-102 group and 0.8% of patients in the placebo group, with the majority of events being Grade ≥ 3 AEs (12.0% versus 0.8%, respectively). AEs resulting in dose reduction reported in ≥ 1% of patients in the TAS-102 group (vs placebo) were neutropaenia (3.2% versus 0%), anaemia (2.1% versus 0.4%), febrile neutropaenia (1.9% versus 0%), neutrophil count decreased (1.9% versus 0%), fatigue (1.5% versus 0%), and diarrhoea (1.3% versus 0%).

9.2.11. Treatment interruptions/delay or reduction due to AEs

AEs resulting in interruption/delay or reduction of study medication were reported in 54.2% of patients in the TAS-102 group and 13.6% of patients in the placebo group, with the majority of events in both treatment groups being Grade ≥ 3 AEs (38.5% versus 8.7%, respectively). AEs resulting in interruption/delay or reduction of study medication reported in ≥ 1% of patients in the TAS-102 group (vs placebo) were neutrophil count decreased (20.5% versus 0.4%), neutropaenia (19.9% versus 0%), anaemia (5.4% versus 0.8%), fatigue (3.0% versus 0.4%), pyrexia (2.8% versus 1.1%), diarrhoea (2.4% versus 0%), febrile neutropaenia (2.1% versus 0%), nausea (1.9% versus 0.4%), vomiting (1.9% versus 0%), decreased appetite (1.7% versus 1.9%), WBC decreased (1.5% versus 0%), asthenia (1.3% versus 0.8%), platelet count decreased (1.3% versus 0%), and abdominal pain (1.1% versus 0.8%).

9.2.12. Clinical laboratory

Laboratory haematological Grade ≥ 3 abnormalities were reported more frequently in patients in the TAS-102 group than in the placebo group for the following parameters - neutropaenia (37.9% versus 0%), lymphocytopaenia (21.5% versus 10.0%), leukopaenia (21.4% versus 0%), anaemia (18.2% versus 3.0%), and thrombocytopaenia (5.1% versus 0.4%). The only laboratory clinical chemistry abnormality of note was a greater incidence of hyperglycaemia ≥ Grade 3 in patients in the TAS-102 group compared to the placebo group (6.4% versus 2.8%). There were no marked differences between the two treatment groups as regards the patient incidence of hepatobiliary clinical chemistry abnormalities, and no evidence of drug induced liver injury associated with TAS-102. There were no marked differences between the two treatment groups as regards the patient incidence of renal clinical chemistry abnormalities, and no evidence that TAS-102 is associated with renal toxicity. However, proteinuria (all grades) was reported more commonly in patients in the TAS-102 group than in the placebo group (4.1% versus 1.9%).

9.2.13. Vital signs and ECG

No significant changes in vital sign or ECG parameters (including QTc prolongation) were reported to be associated with treatment with TAS-102.

9.2.14. Special groups

There was an increased risk of AEs in patients aged ≥ 65 years of age treated with TAS-102 compared to patients aged < 65 years. In the TAS-102 group, patients aged ≥ 65 years had a higher incidence (difference of at least 5%) compared to patients aged < 65 years of anaemia (50.4% versus 32.1%), neutropaenia (32.9% versus 26.4%), neutrophil count decreased (31.2% versus 25.1%), platelet count decreased (21.4% versus 10.4%), white blood cell count decreased (31.6% versus 24.1%) and decreased appetite (41.9% versus 36.8%). Based on clinical laboratory

assessments, patients aged ≥ 65 years in the TAS-102 group had a higher incidence than patients aged < 65 years (difference of at least 5%) of Grade 3 or 4 leukopaenia (25.5% versus 18.2%), Grade 3 or 4 neutropaenia (47.6% versus 30.3%), Grade 3 anaemia (26.0% versus 12.1%) and Grade 3 or 4 thrombocytopaenia (8.7% versus 2.4%).

In the TAS-102 group, females had a higher incidence (difference of at least 5%) compared to male patients of anaemia (44.9% versus 37.1%), abdominal pain (18.4% versus 12.6%), abdominal pain upper (12.1% versus 4.0%), diarrhoea (37.2% versus 28.5%), nausea (55.1% versus 44.2%), vomiting (42.0% versus 18.7%), back pain (11.6% versus 5.5%), and cough (14.0% versus 8.6%). Based on clinical laboratory assessments, female patients who received TAS-102 had a higher incidence than male patients (difference of at least 5%) of Grade 3 or 4 leukopaenia (24.6% versus 19.4%), Grade 3 or 4 neutropaenia (42.9% versus 34.8%), Grade 3 or 4 lymphocytopaenia (24.9% versus 19.3%) and Grade 3 anaemia (23.2% versus 15.1%), with a similar incidence of Grade 3 or 4 thrombocytopaenia (4.4% versus 5.5%).

There were differences in the safety profile of TAS-102 between Western and Asian patients, which the sponsor suggests indicates differences in reporting patterns between Western and Asian geographical regions. The sponsor postulates that the observed differences probably reflect subtle regional differences in the usage of terms (e.g., asthenia versus fatigue) as well as cultural differences that influence how patients report events.

In the TAS-102 group, Grade ≥ 3 AEs were reported in ≥ 5% more patients with moderate renal impairment (CLcr 30-59 mL/min) compared to patients with normal renal function or mild renal impairment (CLcr 60-89 mL/min (that is, 85.1% versus 66.7% versus 70.8%, respectively), as were treatment related Grade ≥ 3 AEs (that is, 61.7% versus 52.8% versus 45.1%, respectively) and SAES (that is, 42.6% versus 30.3% versus 27.5%, respectively). The incidence of dose reductions was increased in patients with renal impairment (that is, 10.8%, 16.3%, and 23.4%, for normal renal function, mild renal impairment, and moderate renal impairment respectively. There were no safety data in patients with severe renal impairment or ESRD. There were no safety data in patients with hepatic impairment.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of TAS-102, given the proposed usage, is favourable. In the pivotal study (RECOURSE), there was a modest statistically significant improvement in median OS of 1.8 months in the TAS-102 group compared to the placebo group at the date of the primary analysis, and 2.0 months at the time of the updated analysis. In addition there was a small statistically significant improvement in median PFS of 0.3 months of doubtful clinical significance in the TAS-102 group compared to the placebo group.

Balanced against the modest benefit in OS, there was a marked increase in the risks of myelosuppression, nausea, vomiting, diarrhoea and infection in patients in the TAS-102 group compared to placebo. However, the adverse events associated with TAS-102 were generally manageable by dose interruption/delay or reduction rather than treatment discontinuation. Fatal AEs occurred uncommonly in patients in the TAS-102 group and were more frequent in patients in the placebo group. Overall, the benefit-risk profile of TAS-102 should be interpreted in the context of its proposed usage for patients with mCRC who have been previously treated with standard available therapies.

10. First round recommendation regarding authorisation

It is recommended that trifluridine/tipiracil be 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.

11. Clinical questions

11.1. Pharmacokinetics

1. Please indicate when the TGA can expect to receive the dedicated renal impairment and dedicated hepatic impairment studies.
2. TPI is metabolised primarily to 6-hydroxymethyl uracil (6-HMU). Please identify the sites and mechanisms involved in this transformation.

11.2. Safety

3. In the pivotal study (RECOURSE), the total number of weeks of exposure was approximately 4-fold longer in the TAS-102 group than in the placebo group (6743 versus 1791 weeks respectively). No safety data could be identified in the study report comparing safety outcomes in the two treatment groups adjusted for duration of exposure. Please justify the absence of pivotal comparative safety data (RECOURSE) adjusted for duration of exposure.
4. In the pivotal study (RECOURSE), proteinuria (all grades) was reported more commonly in patients in the TAS-102 group than in the placebo group (4.1% versus 1.9%). Please comment on the possible reasons for this imbalance.

12. Second round evaluation of clinical data

12.1. Pharmacokinetics

12.1.1. Question 1

Please indicate when the TGA can expect to receive the dedicated renal impairment and dedicated hepatic impairment studies.

12.1.1.1. Sponsor Response

The sponsor's post-first round response included the clinical study report for the dedicated hepatic impairment Study TO-TAS-102-106. The sponsor states that '(b)ased on the study results, changes to the EU SmPC (were) proposed to the EMA in November 2016 and are also proposed to the TGA with the [post first-round] response'. The sponsor stated that the dedicated renal impairment study is due to be completed by September 2017 with a study report by December 2017.

12.1.1.2. Evaluation of response

The sponsor's response is satisfactory. The dedicated hepatic impairment study has been evaluated and the results are reported immediately below. The sponsor is requested to submit the report for the dedicated renal impairment study to the TGA when it is finalised.

12.1.2. Evaluation of the dedicated hepatic impairment study

12.1.2.1. Title, location and dates

Phase I, open-label study which aims to evaluate the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment (TO-TAS-102-106).

The study was undertaken at 7 centres in the USA between 23 February 2015 and 4 April 2016, and the final study report was dated 26 October 2016. The study was sponsored by Taiho Oncology, Inc. The study is reported to have been conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.

12.1.2.2. Objectives

The primary objectives of the PK Part (Cycle 1) of the study were: (i) to evaluate the impact of hepatic impairment on the PK profile of TAS-102 (FTD and TPI) and FTY (the major metabolite of FTD); and (ii) to assess the safety and tolerability of TAS-102 in advanced solid tumour patients with varying degrees of hepatic impairment.

The exploratory objective of the Extension Part (Cycles ≥ 2) of the study was to assess the safety and tolerability of TAS-102 in advanced solid tumour patients with varying degrees of hepatic impairment in Cycles 2 and beyond.

12.1.2.3. Design

The study was designed as a Phase I, open-label study to evaluate the safety, tolerability, and PK of TAS-102 (FTD and TPI) and FTY (the major metabolite of FTD) in advanced solid tumour patients (excluding breast cancer) with varying degrees of hepatic impairment after single-dose and multiple-dose oral administration. The study was conducted in order to provide specific dosing recommendations for patients with hepatic impairment. The study was conducted in 2 parts (PK Part (Cycle 1) and Extension Part (Cycles ≥ 2)).

In this study, hepatic impairment was based on the National Cancer Institute (NCI) Hepatic Impairment Classification Criteria (see below). In the PK Part (Cycle 1), patients must have fulfilled both total bilirubin and aspartate aminotransferase (AST) criteria to have been included in the relevant study group. However, if a patient's total bilirubin level and AST level indicated different groups, the patient may have been enrolled in the group with the greatest degree of liver dysfunction based on the criteria. No distinction was to be made between liver dysfunction due to metastases and liver dysfunction resulting from other causes.

Table 68: NCI Hepatic Impairment Classification Criteria

Group	

Patients were to be enrolled in 3 parallel Cohorts (0 (normal hepatic function), 1 (mild hepatic impairment), and 2 (moderate hepatic impairment)) according to their baseline hepatic function, with enrolment into a fourth cohort (Cohort 3 (severe hepatic impairment)) being dependent on the results of an interim assessment of safety, tolerability and PK in cohorts 0, 1, and 2. Approximately 8 patients were to be enrolled in each cohort to ensure a sufficient number (approximately 6) of evaluable patients. No patients were enrolled in Cohort 3 (severe hepatic impairment) due to the study being discontinued because of the high incidence of Grade 3 or 4 increased bilirubin levels in patients in Cohort 2 (moderate hepatic impairment).

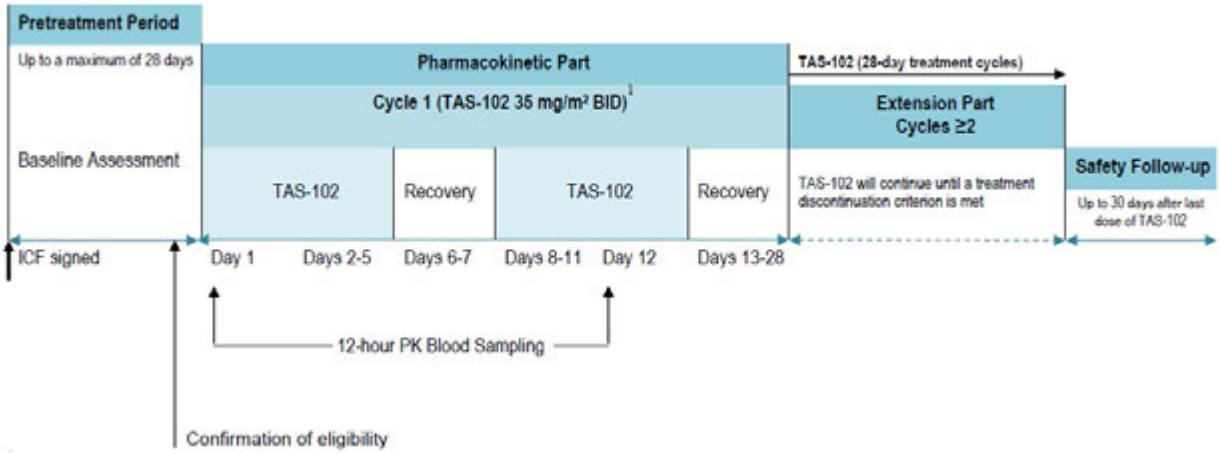
Each treatment cycle was 28 days in duration. During the PK Part (Cycle 1), patients in Cohorts 0, 1, and 2 received the recommended oral dose of TAS-102, 35 mg/m^2, BD based on BSA. TAS-102 was administered orally BD on Days 1 through 5 of Cycle 1 one hour after completing a morning and evening meal, followed by a recovery period from Days 6 through 7. TAS-102 was administered BD again on Days 8 through 12, with the last dose administered in the evening of Day 12, followed by a recovery period from Days 13 through 28. On Day 1 and Day 12, patients received both morning and evening doses of TAS-102 and blood samples for PK analysis were collected at pre-specified time-points. The primary milestone for analysis and reporting of the final study results was the end of the PK Part (Cycle 1) of the study.

Patients who completed the PK Part (Cycle 1) of the study were eligible to enter the Extension Part (Cycles ≥ 2) during which TAS-102 was administered orally BD for 5 days with 2 days rest for 2 weeks, repeated every 4 weeks until the patient met any of the treatment discontinuation criteria. For each patient, the TAS-102 dose was to be the same as that received in Cycle 1, unless dose modification was required because of toxicity based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Safety was assessed by AEs, concomitant medications, complete physical examination results, ECOG PS, vital sign measurements, and laboratory evaluations. Only data associated with safety assessments were to be collected during the Extension Part of the study. Safety monitoring was to begin at the time of a signed and dated ICF and was to continue for 30 days after the last dose of study medication or until a new anticancer treatment was started, whichever occurred first.

The study was to continue until all patients discontinued from treatment or for 12 months after the first dose of TAS-102 (Day 1, Cycle 1) for the last patient enrolled, whichever occurred first. Patients continuing to benefit from treatment with TAS-102 were eligible to continue treatment with the drug beyond completion of the study. However, enrolment into the study was stopped on 15 April 2016 for safety reasons as 5 of the 6 patients in the moderate hepatic impairment cohort experienced Grade 3 or 4 increased blood bilirubin levels. Therefore, no patients with severe hepatic impairment were enrolled into the study. The pre-specified study flow is presented schematically below.

Figure 13: Pre-specified study flow



The dose level for Cohort 3 (severe hepatic impairment) may be reduced if warranted by the IA results for Cohorts 0, 1, and 2. Abbreviations: BID = twice daily; IA = interim assessment; ICF = informed consent form; PK = pharmacokinetic.

12.1.2.4. Study population

The planned study population included male and female patients aged ≥ 18 years with confirmed advanced solid tumours (except breast cancer) and normal hepatic function (Cohort 0) or varying degrees of hepatic impairment (Cohorts 1, 2, and 3). Patients must have failed or been intolerant to standard anticancer therapy. Baseline ECOG PS was required to be ≤ 2. Patients were also required to have adequate haematological and renal function. The study included a number of pre-defined exclusion criteria, including pre-existing and concurrent medical conditions and medical treatments. The inclusion and exclusion criteria have been examined and are considered to be satisfactory. The study also included satisfactory pre-specified criteria for discontinuation from study treatment.

12.1.2.5. Pharmacokinetic (PK) assessments

On Day 1 and Day 12 of Cycle 1, blood samples were collected from all patients for measurement of plasma concentrations of TAS-102 (FTD and TPI) and FTY (the major metabolite of FTD). Blood

samples were collected 30 minutes prior to the morning dose (0 hour) and then at 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose. No concentration estimates were provided for missing samples, with the exception of imputation of the pre-dose value as this was required for the AUC calculation. Satisfactory procedures were in place for handling samples with plasma concentrations below the LLOQ.

PK analysis for FTD, FTY, and TPI in plasma following administration of TAS-102 on Day 1 and Day 12 of Cycle 1 included the parameters listed below calculated by standard non-compartmental methods.

- Cmax: Maximum observed plasma concentration.
- Tmax: Time to maximum observed plasma concentration.
- AUC0-last: Area under the plasma concentration-time curve from time 0 to the last measurable plasma concentration estimated by linear trapezoidal rule.
- RCmax: Accumulation ratio calculated as ratio of Cmax (Day12)/Cmax (Day 1).
- RAUC0-last: Accumulation ratio calculated as ratio of AUC0-last (Day12)/AUC0-last (Day 1).
- T1/2: Apparent terminal phase elimination half-life = ln(2)/λz.
- AUC0-inf: Area under the plasma concentration-time curve from time 0 to infinity calculated for Day 1 only as follows: AUC0-inf = AUC0-last + Clast/λz, where Clast was the last measurable plasma concentration and λz was the terminal elimination rate constant after the AM dose estimated using log-linear regression during the elimination phase. The points used in the λz calculation were determined by visual inspection of the data describing the elimination phase and at least the last 3 time points were used in λz calculations.
- AUCtau = AUC0-12: Area under the plasma concentration-time curve from time 0 to the end of dosing interval for Day 12 only.

In addition, the apparent clearance (CL/F) and apparent volume of distribution (Vd/F) were calculated for FTD and TPI (but not for FTY) using the following equations:

- CL/F = Dose / AUC0-inf (for Day 1).
- CLss/F (Steady state oral clearance) = Dose/AUCtau (for Day 12).
- Vd/F = (CL/F)/λz (for Day 1).

The PK population included all patients in the As Treated population with evaluable PK profiles on either Day 1 or Day 12, or both days, of Cycle 1. The As Treated population included all patients who received at least 1 dose of TAS-102. Estimation of PK parameters in the PK population was performed using PhoenixTM WinNonlin® (Certara L.P.), version 6.4 software. The concentrations of FTD, FTY, and TPI in plasma were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

12.1.2.6. Analysis of hepatic impairment on the PK of TAS-102

The sponsor stated that the typical sample size for estimation of PK in hepatic impairment studies is 6 evaluable patients per cohort. Taking into account the individual variability in PK parameters (maximum percent CV 50%) and assuming a 25% dropout rate, approximately 8 patients per cohort were to be enrolled to obtain approximately 6 evaluable patients per cohort.

The endpoints for comparison of the hepatic impairment cohorts (Cohorts 1 and 2) to the normal hepatic function cohort (Cohort 0) were Cmax, AUC0-inf and AUCtau for FTD, FTY, and TPI, and CL/F (Day 1) and CLss/F (Day 12) for FTD and TPI. Other PK parameters were summarised as additional endpoints for FTD, TPI, and FTY.

The Cmax, AUC0-last, AUC0-inf, and AUCtau for FTD, FTY, and TPI and CL/F (Day 1) and CLss/F (Day 12) for FTD and TPI were analysed by ANOVA using the categorical hepatic impairment

cohorts as class variables after the parameters had been log transformed. Comparisons were made between the normal hepatic function cohort (Cohort 0) and each hepatic impairment cohort (Cohorts 1 and 2). Point estimates with corresponding 90% CIs were constructed and then back-transformed from the log-scale to express the estimates as ratios of each hepatic impairment cohort relative to the normal hepatic function cohort.

The relationship between the PK parameters of interest (AUC0-last, AUC0-inf, AUCtau, and Cmax for FTD, FTY, and TPI) and AST or total blood bilirubin (TBL) were assessed by regression analysis using the power model expressed by the equation, log(PK parameters) = α+β log(AST or TBL). The model used the log transformed PK parameter as the dependent variable and the log of the AST or TBL as the independent variable. This model was used to investigate the null hypothesis (H0: β=0), with the null hypothesis not being rejected if the 90% CI for β included 1. For these analyses, the PK parameters of interest were the AUC0-last, AUC0-inf, and Cmax obtained on Day 1 of Cycle 1 (single-dose) and the AUC0-last, AUCtau, and Cmax obtained on Day 12 of Cycle 1 (multiple-dose, steady state). The same analysis was applied for CL/F (Day 1), CLss/F (Day 12), and Vd/F (Day 1) of FTD and TPI.

Accumulation parameters, RCmax and RAUC0-last of FTD, FTY, and TPI were log transformed and analysed by one-way ANOVA. Comparisons were made between the normal hepatic function cohort (Cohort 0) and each hepatic impairment cohort (Cohorts 1 and 2). Point estimates with corresponding 90% CIs were constructed and then back-transformed from the log-scale to express the estimates as ratios of each hepatic impairment cohort relative to the normal hepatic function cohort.

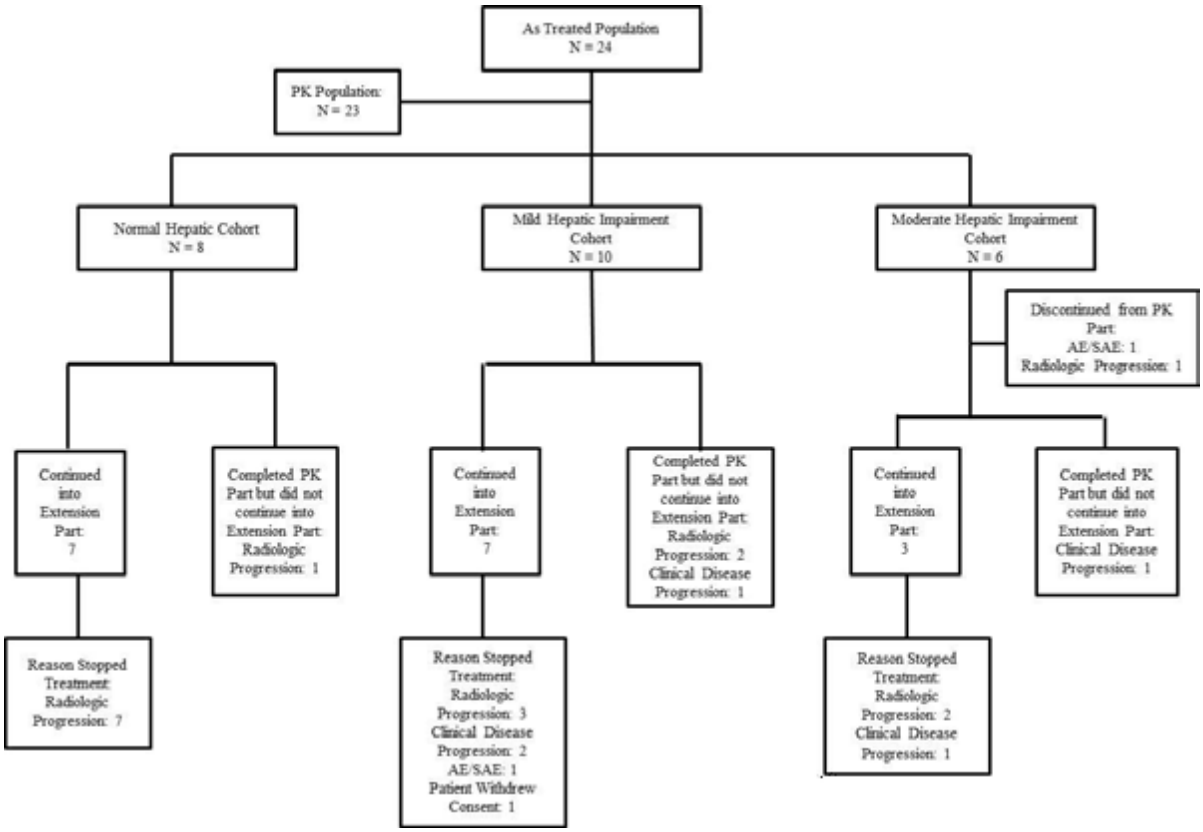
No statistical hypotheses were tested in this study for the comparison between the PK of patients with normal hepatic function (Cohort 1) and patients with hepatic impairment (Cohorts 1 and 2). Therefore, no statistical adjustments were undertaken for the multiplicity of pairwise PK comparisons.

12.1.2.7. Patient disposition

A total of 24 patients were enrolled and received at least 1 dose of study medication, comprising 8 patients in the normal hepatic function cohort, 10 patients in the mild hepatic impairment cohort, and 6 patients in the moderate hepatic impairment cohort. Of the 24 patients enrolled in the PK Part (Cycle 1), 2 patients (8.3%) in the moderate hepatic impairment cohort discontinued treatment during Cycle 1 (that is, SAE of increased bilirubin in 1 patient, radiologic disease progression in 1 patient). A total of 23 patients (95.8%) were evaluable for PK assessment (PK Population) in Cycle 1.

Of the 22 patients who completed Cycle 1, 5 patients (20.8%) did not enter the Extension Part (Cycles ≥ 2) because of either radiologic or clinical disease progression. These 5 patients included 1 patient in the normal hepatic function cohort, 3 patients in the mild hepatic impairment cohort, and 1 patient in the moderate hepatic impairment cohort. Therefore, a total of 17 patients (70.8%) entered the Extension Part (Cycles ≥ 2). Of the 17 patients who entered the Extension Part (Cycles ≥ 2), 15 patients discontinued treatment because of disease progression (clinical or radiological), 1 patient discontinued due to AEs of neutropaenia and thrombocytopaenia and 1 patient withdrew consent. No patients were ongoing in the Extension Part at the time of the analysis. The patient disposition of the As Treated population (n = 24) is summarised below.

Figure 14: Patient disposition, As Treated population



12.1.2.8. Baseline demographic characteristics

The median age of the total population (n = 24) was 60.5 years (range: 33, 77 years), with the median age across the three treatment cohorts ranging from 48.5 years (mild hepatic impairment) to 64 years (normal hepatic function). The genders were relatively evenly distributed in the total population (54.2% (n = 13), male; 45.8% (n = 11), female), and were evenly distributed (50%/50%) in the normal hepatic function and mild hepatic impairment cohorts but not in the moderate hepatic impairment cohort (66.7% (n = 4), male; 33.3% (n = 2), female). Most of the patients in the total population were categorised as White (83.3% (n = 20)), with 2 (8.3%) patients being categorised as Black or African American and 2 (8.3%) patients being categorised as Asian.

The median height of the total population (n = 23) was 166.5 cm (range: 150, 187), with no marked differences in median height across the three treatment cohorts. The median weight of the total population (n = 24) was 73 kg (range: 42, 130), with no marked differences in median weight across the three treatment cohorts. The median BSA of the total population (n = 24) was 1.82 m^2 (range: 1.32, 2.38), with no marked differences in median BSA across the three treatment cohorts.

The median (range) bilirubin (µmol/L) values for the normal hepatic function (n = 8), mild hepatic impairment (n = 10), and moderate hepatic impairment (n = 6) cohorts were 8.550 (3.42, 13.68), 11.970 (6.84, 25.65) and 49.590 (27.36, 59.85) µml/L, respectively. The median (range) AST (U/L) values for the normal hepatic function (n = 8), mild hepatic impairment (n = 10), and moderate hepatic impairment (n = 6) cohorts were 26 (17, 39), 57 (26, 78) and 65 (38, 95) U/L, respectively.

12.1.2.9. Baseline cancer type and prior therapies

Of the 24 patients in the total population, 9 had colorectal carcinoma, 5 had pancreatic cancer, 4 had biliary cancer, 2 had prostate cancer, and the remaining 4 had ovarian cancer, pelvic cancer (histologically reported as a carcinoid tumour), duodenal cancer, or unknown primary (histologically reported as a carcinoma and clinically suspected pancreatic or biliary tumour). At the time of enrolment, 23 of the 24 patients had metastatic cancer. Prior radiation therapy had been received by 2 of the 8 patients in the normal hepatic function cohort, 9 of the 10 patients in

the mild hepatic impairment cohort and 2 of the 6 patients in the moderate hepatic impairment cohort. Prior treatment with anticancer therapy had been received by 23 of the 24 patients. Prior anticancer therapies included metastatic, adjuvant, neoadjuvant, or combination anticancer treatments, and ranged from 1 to 7 regimens.

12.1.2.10. Common concomitant medications taken during the study

The most commonly reported (≥ 15%) (excluding uncoded) concomitant medications continued or started after the first dose of study medication in the total population were serotonin (5HT3) antagonists (79.2%), natural opium alkaloids (70.8%), proton pump inhibitors (50%), anilides (33.3%),heparin group (33.3%), other blood products (packed red blood cells, red blood cells, platelets, and frozen plasma transfusions) (29.2%), other antidepressants (29.2%), contact laxatives (25%), carbapenems (25%), osmotically acting laxatives (20.8%), thyroid hormones (20.8%), third generation cephalosporins (16.7%), benzodiazepine derivatives (16.7%), ACE inhibitors plain (16.7%), antipropulsives (16.7%), vitamin D and analogues (16.7%), colony stimulating factors (16.7%), and HMG COA reductase inhibitors (16.7%).

12.1.2.11. PK Results

Plasma concentration time profiles

PK blood samples were collected on Day 1 and Day 12 of Cycle 1.

Evaluator's comment

The mean plasma elimination phase concentration of FTD on Day 1, Cycle 1 was similar in patients with mild or moderate hepatic impairment, while the corresponding plasma concentration in patients with normal hepatic function was higher than in patients in both hepatic impairment cohorts. The mean plasma elimination phase concentration of FTD at steady state (Cycle 1, Day 12) was lower in patients with moderate hepatic impairment compared to patients with normal hepatic function and mild hepatic impairment. The mean plasma elimination phase concentration of FTY on Day 1, Cycle 1 was similar in patients with mild or moderate hepatic impairment, while the corresponding plasma concentration in patients with normal hepatic function was higher than in patients in both hepatic impairment cohorts. The mean plasma elimination phase concentration of FTY at steady state (Cycle 1, Day 12) was comparable in the three treatment cohorts. The mean plasma elimination phase concentration of TPI on Day 1, Cycle 1 was comparable in patients with normal hepatic function and moderate hepatic impairment, and higher in both cohorts than in patients with mild hepatic impairment. At steady state (Cycle 1, Day 12), the mean plasma elimination phase concentration of TPI was comparable in the 3 treatment cohorts.

Pharmacokinetic parameters

PK parameters were calculated for FTD, TPI, and FTY in plasma after administration of TAS-102 on Day 1 and Day 12 of Cycle 1 according to the non-compartmental method.

Evaluator's comment

Mean $AUC_{0\text{-}inf}$ FTD values in Cycle 1, Day 1 decreased with increasing hepatic impairment (that is, 6873, 6324, and 4594 ng.hr/mL for normal hepatic function, mild hepatic impairment, and moderate hepatic impairment, respectively). This trend was also observed at steady state (Cycle 1, Day 12) for mean AUC_{tau} FTD values (that is, 20392, 17489, 15406 ng.hr/mL for normal hepatic function, mild hepatic impairment, and moderate hepatic impairment, respectively). The steady state AUC_{tau} FTY value was greater in patients with moderate hepatic impairment (5172 ng.hr/mL) than in patients with normal hepatic function (4833 ng.hr/mL) and patients with mild hepatic impairment (3516 ng.hr/mL). The sponsor comments that the increased AUC_{tau} FTY value at steady state in the moderate hepatic impairment cohort compared to the other two treatment cohorts might be due to the limited sample size (n = 3) and high inter-subject variability of AUC_{tau} (CV=63.8%) FTY in patients with moderate hepatic impairment.

The mean $AUC_{0\text{-}inf}$ TPI value in Cycle 1, Day 1 was lower in patients with mild hepatic impairment (272 ng.hr/mL) and higher in patients with moderate hepatic impairment (591 ng.hr/mL) than in

patients with normal hepatic function (421 ng.hr/mL). This trend was consistent for AUC_{tau} TPI values in Cycle 1 Day 12, with mean values being 335, 305, and 495 ng.hr/mL for patients with normal renal function, mild hepatic impairment and moderate hepatic impairment, respectively.

The accumulation ratio of C_{max} for FTD at steady state (Cycle 1, Day 12) was 2.43, 1.19, and 2.12 for patients with normal hepatic function, mild hepatic impairment and moderate hepatic impairment, respectively, and the corresponding accumulation ratios for $AUC_{0\text{-}last}$ for FTD were 2.85, 2.53, and 3.42, respectively. No marked differences were observed across the three treatment cohorts for the accumulation ratios of C_{max} and $AUC_{0\text{-}last}$ for FTY or TPI at steady state (Cycle 1, Day 12).

Statistical analysis of pharmacokinetic parameters

The C_{max} (Days 1 and 12), $AUC_{0\text{-}inf}$ (Day 1), AUC_{tau} (Day 12), CL/F (Day 1), and CLss/F (Day 12) for FTD and TPI were analysed by a one-way ANOVA. Comparisons were made between each of the two hepatic impairment cohorts and the normal hepatic function cohort.

The results for FTD are summarised below.

Table 69: Effect of hepatic impairment (one-way ANOVA) for FTD PK Parameters, PK Population

		Normal	Mild HI	Moderate HI
Cycle 1, Day 1		*n = 7*	*n = 7*	*n = 5*
Cmax	GM	2090	2982	1623
(ng/mL)	GMR to Normal	-	1.43 (90% CI: 0.84, 2.43)	0.78 (95% CI: 0.43, 1.39)
	p value for GMR	-	p = 0.2611	p = 0.4609
AUC0-inf	GM	6511	5981	4379
(ng.hr/mL)	GMR to Normal	-	0.92 (90% CI: 0.66, 1.29)	0.67 (90% CI: 0.46, 0.79)
	p value for GMR	-	p = 0.6664	p = 0.0792
CL/F	GM	8.95	10.34	14.55
(L/hr)	GMR to Normal	-	1.16 (90% CI: 0.79, 1.68)	1.63 (90% CI: 1.08, 2.45)
	p value for GMR	-	p = 0.4426	p = 0.9981
Cycle 1, Day 12		*n = 7 or 8 **	*n = 8*	*n = 3*
Cmax	GM	4277	3716	4275
(ng/mL)	GMR to Normal	-	0.87 (90% CI: 0.64, 1.19)	1.00 (90% CI: 0.66, 1.52)
	p value for GMR	-	p = 0.4426	p = 0.9981
AUCtau	GM	19761	16246	15372
(ng.hr/mL)	GMR to Normal	-	0.82 (90% CI: 0.61, 1.11)	0.78 (90% CI: 0.52, 1.16)
	p value for GMR	-	p = 0.2729	p = 0.2908
CLss/F	GM	3.01	3.94	4.33
(L/hr)	GMR to Normal	-	1.31 (90% CI: 0.95, 1.80)	1.44 (90% CI: 0.94, 2.20)

		Normal	Mild HI	Moderate HI
	p value for GMR	-	p = 0.1624	p = 0.1562

* Cmax, AUCtau, CLss/F: n = 8, 7, and 7, respectively, for normal hepatic function. Abbreviations: ANOVA = analysis of variance; AUC0-inf = area under the plasma concentration-time curve from time 0 to infinity; AUCtau = area under the plasma concentration-time curve from time 0 to the end of dosing interval for Day 12; CI = confidence interval; CL/F = oral clearance following single-dose; CLss/F = oral clearance at steady state; Cmax = maximum observed plasma concentration; FTD = trifluridine; GM = geometric mean; GMR = geometric mean ratio of test to reference; hr = hour; PK = pharmacokinetic.

Evaluator's comment

The results for FTD at steady state (Cycle 1, Day 12) suggest that the observed differences in peak exposure (based on Cmax values) and systemic exposure (based on AUCtau values) between patients with normal hepatic function and patients with either mild or moderate hepatic impairment are unlikely to be clinically meaningful. However, the PK results for the comparison between patients with normal hepatic function and moderate hepatic impairment should be interpreted cautiously due to the small number of patients (n = 3) in the moderate hepatic impairment cohort.

No statistically significant differences were observed for Cmax (Cycle 1, Days 1 and 12), AUCinf (Cycle 1, Day 1), AUCtau (Cycle 1, Day 12), CL/F (Cycle 1, Day 1) or CLss/F (Cycle 1, Day 12) between patients with normal hepatic function and patients with either mild or moderate hepatic impairment. Peak exposure based on mean geometric Cmax values was 43% higher in patients with mild hepatic impairment compared to patients with normal hepatic function in Cycle 1, Day 1, but 13% lower in Cycle 1, Day 12. Peak exposure based on mean geometric Cmax values was 22% lower in patients with moderate hepatic impairment compared to patients with normal hepatic function in Cycle 1, Day 1, and almost identical in Cycle 1, Day 12. Systemic exposure at steady state (Cycle 1, Day 12) based on geometric mean AUCtau values was 18% lower in patients with mild hepatic impairment and 22% lower in patients with moderate hepatic impairment compared to patients with normal hepatic function. While there were no statistically significant differences in AUCtau values between the normal hepatic function cohort and both the mild and moderate hepatic impairment cohorts, the 90% CI were not enclosed entirely within the conventional bioequivalence interval of 0.80 to 1.25.

The results for TPI are summarised below.

Table 70: Effect of hepatic impairment (one-way ANOVA) for TPI PK Parameters, PK Population

		Normal	Mild HI	Moderate HI
Cycle 1, Day 1		n = 6-7 *	n = 6-7 *	n = 4-5 *
Cmax (ng/mL)	GM	63.82	57.00	78.69
	GMR to Normal	-	0.89 (90% CI: 0.51, 1.58)	1.23 (90% CI: 0.66, 2.30)
	p value for GMR		p = 0.7330	p = 0.5653
AUC0-inf (ng.hr/mL)	GM	383.39	247.04	462.64
	GMR to Normal	-	0.64 (90% CI: 0.35, 1.18)	1.21 (90% CI: 0.61, 2.38)
	p value for GMR	-	p = 0.2216	p = 0.6316
CL/F	GM	71.20	120.19	67.31

		Normal	Mild HI	Moderate HI
(L/hr)	GMR to Normal	-	1.69 (90% CI: 0.86, 3.32)	0.95 (90% CI: 0.44, 2.02)
	p value for GMR	-	p = 0.1946	p = 0.8975
Cycle 1, Day 12		n = 7-8 **	n = 7-8 **	n = 3
Cmax	GM	57.38	56.68	82.97
(ng/mL)	GMR to Normal	-	0.99 (90% CI: 0.59, 1.65)	1.45 (90% CI: 0.72, 2.90)
	p value for GMR	-	p = 0.9673	p = 0.3678
AUCtau	GM	287.23	287.35	420.36
(ng.hr/mL)	GMR to Normal	-	1.00 (90% CI: 0.61, 1.65)	1.46 (90% CI: 0.77, 2.78)
	p value for GMR	-	p = 0.9988	p = 0.3147
CLss/F	GM	97.64	102.60	74.65
(L/hr)	GMR to Normal	-	1.05 (90% CI: 0.58, 1.90)	0.76 (90% CI: 0.35, 1.65)
	p value for GMR	-	p = 0.8854	p = 0.5478

* Cmax, AUC0-inf, CL/F: n = 7, 6, respectively, for normal hepatic function and mild hepatic impairment cohorts; and n = 5, 5, 4, respectively for moderate hepatic impairment. ** Cmax, AUCtau, CLss/F: n = 8, 7, 7, respectively, for normal hepatic function and mild hepatic impairment cohorts. Abbreviations: ANOVA = analysis of variance; AUC0-inf = area under the plasma concentration-time curve from time 0 to infinity; AUCtau = area under the plasma concentration-time curve from time 0 to the end of dosing interval for Day 12 only; CI = confidence interval; CL/F = oral clearance following single dose; CLss/F = oral clearance at steady state; Cmax = maximum observed plasma concentration; TPI = tipiracil; GM = geometric mean GMR = geometric mean ratio of test to reference; hr = hour; PK = pharmacokinetic.

Evaluator's comment

The results for TPI suggest that the observed differences in peak exposure (based on Cmax values) and systemic exposure (based on AUC values) between patients with normal hepatic function and patients with mild hepatic impairment are unlikely to be clinically meaningful following single- and multiple-dosing with TAS-102. However, both peak exposure (based Cmax values) and systemic exposure (based on AUC values) were greater in patients with moderate hepatic impairment compared to patients with normal hepatic function following both single- and multiple-dosing. In the moderate hepatic impairment cohort, the results for systemic exposure to TPI at steady state based on the AUCtau should be interpreted cautiously due to the small sample size (n = 3) and the high inter-subject variability (CV%=58.1%).

No statistically significant differences were observed for C_{max} (Cycle 1, Days 1 and 12), AUCinf (Cycle 1, Day 1), AUC_{tau} (Cycle 1, Day 12), CL/F (Cycle 1, Day 1) or CLss/F (Cycle 1, Day 12) between patients with normal hepatic function and patients with either mild or moderate hepatic impairment. Peak exposure based on mean geometric C_{max} values was 11% lower in patients with mild hepatic impairment compared to patients with normal hepatic function in Cycle 1, Day 1, and almost identical in the two treatment groups in Cycle 1, Day 12. Peak exposure based on mean geometric C_{max} values was 23% higher in patients with moderate hepatic impairment compared to patients with normal hepatic function in Cycle 1, Day 1, and 45% higher in Cycle 1, Day 12. Systemic exposure at steady state (Cycle 1, Day 12) based on geometric mean AUC_{tau} values was almost identical in patients with mild hepatic impairment and normal hepatic function, and 46%

higher in patients with moderate hepatic impairment compared to patients with normal hepatic function. While there were no statistically significant differences in AUC_{tau} values between the normal hepatic function cohort and both the mild and moderate hepatic impairment cohorts, the 90% CI were not enclosed entirely within the conventional bioequivalence interval of 0.80 to 1.25.

12.1.2.12. Regression analysis of PK parameters with hepatic function tests

The relationships between oral clearance (CL/F for Day 1, CLss/F for Day 12) for FTD and TPI, and baseline aspartate transferase (AST) and total bilirubin levels (TBL) were assessed by regression analysis using power models. The models used the log transformed PK parameters as the dependent variable and the log of the AST or TBL as the independent variable. No significant relationships were observed between the clearance (CL/F and CLss/F) of FTD or TPI and liver function parameters AST or TBL.

12.1.2.13. Relationship between AUC0-last (FTD and TPI) and Grade 3/4 TBL increased

No trend was seen for individual PK parameters of FTD or TPI in patients with Grade 3 or Grade 4 increased TBL. Grade 3 or Grade 4 increased TBL were not associated with increased FTD or TPI exposure.

12.1.2.14. Safety results

Safety data were presented for a total of 24 patients in the total population, comprising 8 patients in the normal hepatic function cohort, 10 patients in the mild hepatic impairment cohort and 6 patients in the moderate hepatic impairment cohort. The mean total dosage of TAS-102 was highest in the mild impairment cohort (1590 mg/m^2) followed by the normal hepatic function cohort (1265 mg/m^2) and the moderate hepatic impairment cohort (947 mg/m^2). The mean treatment duration was longest for the mild hepatic impairment cohort (70.4 days) followed by the normal hepatic function cohort (48.5 days) and the moderate hepatic impairment cohort (32 days). Six of the 24 patients in the total population initiated more than 2 cycles of TAS-102 (2 patients in the normal cohort, 3 patients in the mild hepatic impairment cohort, and 1 patient in the moderate impairment cohort). The remaining patients initiated 1 or 2 cycles of TAS-102. Overall, the maximum number of TAS-102 cycles initiated and completed was 8 cycles in the mild hepatic impairment cohort followed by 4 cycles in the normal hepatic function cohort and 3 cycles in the moderate hepatic impairment cohort.

With the exception of ≥ Grade 3 increased blood bilirubin levels, most of the treatment-related AEs reported during the study were expected effects of treatment with TAS-102. Treatment-related AEs reported in > 10% of patients in the total population were nausea (50%), anaemia (37.5%), fatigue (37.5%), diarrhoea (29.2%), decreased appetite (25%), vomiting (20.8%), neutropaenia (20.8%), decreased neutrophil count (12.5%), decreased white blood cell count (12.5%), and alopecia (12.5%). Patients in the mild hepatic impairment cohort experienced a higher percentage of these treatment-related AEs than patients in the other 2 cohorts. However, both the total dose and the duration of exposure were higher in patients with mild hepatic impairment compared to patients with either normal hepatic function or moderate hepatic impairment. Treatment-related AEs reported in at least 2 (8.3%) patients in the total safety population (n = 24) are summarised below.

Table 71: Summary of treatment-related AEs observed in at least 2 patients in the overall patient population (n = 24) by SOC and PT, As Treated Population

System Organ Class Preferred Term	Normal Cohort (N=8)	Mild Hepatic Impairment Cohort (N=10)	Moderate Hepatic Impairment Cohort (N=6)	Overall (N=24)
Patients with at least one AE	7 (87.5%)	10 (100%)	6 (100%)	23 (95.8%)
GASTROINTESTINAL DISORDERS	6 (75.0%)	9 (90.0%)	3 (50.0%)	18 (75.0%)
Nausea	5 (62.5%)	5 (50.0%)	2 (33.3%)	12 (50.0%)
Diarrhoea	2 (25.0%)	5 (50.0%)	0	7 (29.2%)
Vomiting	1 (12.5%)	4 (40.0%)	0	5 (20.8%)
Dyspepsia	0	1 (10.0%)	1 (16.7%)	2 (8.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (50.0%)	5 (50.0%)	4 (66.7%)	13 (54.2%)
Anaemia	3 (37.5%)	3 (30.0%)	3 (50.0%)	9 (37.5%)
Neutropenia	2 (25.0%)	2 (20.0%)	1 (16.7%)	5 (20.8%)
Lenkopenia	2 (25.0%)	0	0	2 (8.3%)
Thrombocytopenia	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (37.5%)	4 (40.0%)	3 (50.0%)	10 (41.7%)
Fatigue	2 (25.0%)	4 (40.0%)	3 (50.0%)	9 (37.5%)
INVESTIGATIONS	2 (25.0%)	5 (50.0%)	2 (33.3%)	9 (37.5%)
Neutrophil count decreased	1 (12.5%)	2 (20.0%)	0	3 (12.5%)
White blood cell count decreased	0	3 (30.0%)	0	3 (12.5%)
Blood bilirubin increased	0	0	2 (33.3%)	2 (8.3%)
Haemoglobin decreased	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
Lymphocyte count decreased	0	2 (20.0%)	0	2 (8.3%)
Platelet count decreased	0	2 (20.0%)	0	2 (8.3%)
METABOLISM AND NUTRITION DISORDERS	2 (25.0%)	5 (50.0%)	1 (16.7%)	8 (33.3%)
Decreased appetite	2 (25.0%)	4 (40.0%)	0	6 (25.0%)
Hypokalaemia	0	2 (20.0%)	0	2 (8.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	3 (30.0%)	0	3 (12.5%)
Alopecia	0	3 (30.0%)	0	3 (12.5%)

Note: A patient was counted once for each system organ class and once for each preferred term within the system organ class. Percentages were based on number of patients in the As Treated Population within the same cohort.

During the study, CTCAE Grade 3 or higher AEs reported for at least 2 patients in the normal hepatic function cohort were increased blood bilirubin, anaemia, neutropaenia, and abdominal pain (2 of 8 patients (25%) each event). CTCAE Grade 3 or higher AEs reported for at least 2 patients in the mild hepatic impairment cohort were decreased neutrophil count (2 of 10 patients (20%)), decreased white blood cell count (3 of 10 patients (30%)), decreased lymphocyte count (2 of 10 patients (20%)), and hypertension (2 of 10 patients (20%)). CTCAE Grade 3 or higher AEs reported for at least 2 patients in the moderate hepatic impairment cohort were increased blood bilirubin levels (5 of 6 patients (83.3%)) and anaemia (2 of 6 patients (33.3%)). As a result of CTCAE Grade 3 or higher increased blood bilirubin levels experienced by 5 of the 6 patients in the moderate hepatic impairment cohort, enrollment into the study was stopped on 15 April 2016. CTCAE Grade 3 or higher AEs are summarised below.

Table 72: Summary of Grade 3 or higher AEs observed in at least 2 patients in the overall patient population (n = 24) by SOC and PT, As Treated Population

System Organ Class Preferred Term	Normal Cohort (N=8)	Mild Hepatic Impairment Cohort (N=10)	Moderate Hepatic Impairment Cohort (N=6)	Overall (N=24)
Patients with at least one AE	7 (87.5%)	9 (90.0%)	6 (100%)	22 (91.7%)
INVESTIGATIONS	3 (37.5%)	4 (40.0%)	5 (83.3%)	12 (50.0%)
Blood bilirubin increased	2 (25.0%)	0	5 (83.3%)	7 (29.2%)
Neutrophil count decreased	1 (12.5%)	2 (20.0%)	0	3 (12.5%)
White blood cell count decreased	0	3 (30.0%)	0	3 (12.5%)
Lymphocyte count decreased	0	2 (20.0%)	0	2 (8.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (37.5%)	2 (20.0%)	2 (33.3%)	7 (29.2%)
Anaemia	2 (25.0%)	1 (10.0%)	2 (33.3%)	5 (20.8%)
Neutropenia	2 (25.0%)	1 (10.0%)	0	3 (12.5%)
GASTROINTESTINAL DISORDERS	2 (25.0%)	2 (20.0%)	1 (16.7%)	5 (20.8%)
Abdominal pain	2 (25.0%)	1 (10.0%)	0	3 (12.5%)
Small intestinal obstruction	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
VASCULAR DISORDERS	0	3 (30.0%)	0	3 (12.5%)
Hypertension	0	2 (20.0%)	0	2 (8.3%)
METABOLISM AND NUTRITION DISORDERS	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
Hyponatraemia	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (12.5%)	1 (10.0%)	0	2 (8.3%)
Back pain	1 (12.5%)	1 (10.0%)	0	2 (8.3%)

Note: A patient was counted once for each system organ class and once for each preferred term within the system organ class. Percentages were based on number of patients in the As Treated Population within the same cohort.

Three patients (1 in each cohort) died due to disease progression during the study, including 2 patients with both small bowel obstruction and disease progression. In this study, disease progression itself was not considered to be an AE or SAE. One patient in the mild hepatic impairment cohort experienced a fatal Grade 5 AE small intestine obstruction (SAE) considered to be unrelated to treatment with TAS-102 (occurred 28 days after treatment discontinuation).

Overall, 14 (58.3%) patients in the total population (n = 24) reported at least 1 SAE. The percentage of patients with at least 1 SAE was higher in the hepatic impairment cohorts than in the normal hepatic function cohort (that is, 60% (n = 6) mild hepatic impairment versus 66.7% (n = 4) moderate hepatic impairment versus 50% (n = 4), normal hepatic function). SAEs reported for more than 1 patient in the total population (n = 24) included small intestinal obstruction (n = 2 (8.3%); 1 each in the normal hepatic function and mild hepatic impairment cohorts), increased blood bilirubin levels (n = 4 (16.7%); 2 each in the normal hepatic function and moderate hepatic impairment cohorts), hyponatraemia (n = 2 (8.3%); 1 each in the normal hepatic function and mild hepatic impairment cohorts), and deep vein thrombosis (n = 2 (8.3%); both in the mild hepatic impairment cohort).

Only 3 patients reported treatment-related SAEs during the study (2 in the moderate hepatic impairment cohort and 1 in the mild hepatic impairment cohort). In the moderate hepatic impairment cohort, 1 patient reported one treatment-related SAE of increased blood bilirubin levels and 1 patient reported two treatment-related SAEs of increased blood bilirubin levels and bacteraemia. The two SAEs of increased bilirubin levels reported in these patient were considered to be suspected unexpected serious adverse reactions (SUSARs) of Grade 4 intensity and resulted in discontinuation of TAS-102 in both patients. In the mild hepatic impairment cohort, 1 patient reported one treatment-related SAE of hyponatraemia.

AEs leading to study treatment discontinuation were reported in 12 (50%) patients in the total population (n = 24), comprising 2 (25%) patients in the normal hepatic function cohort (1 x fatigue, 1 x neutropaenia), 5 (50%) patients in the mild hepatic impairment cohort (1 x each for device dislocation, neutropaenia, thrombocytopaenia, ascites, small intestinal obstruction, pathological

fracture, sciatica and pelvic pain) and 5 (83.3%) patients in the moderate hepatic impairment cohort (4 x blood bilirubin levels increased, 2 x fatigue, 1 x each for oedema peripheral and bacteraemia).

During the study, 7 patients experienced Grade 3 or 4 increased blood bilirubin, comprising 2 of the 8 patients in the normal hepatic cohort and 5 of the 6 patients in the moderate hepatic impairment cohort. Both of the 2 cases of Grade 3 or 4 increased blood bilirubin levels in the normal hepatic function cohort were considered to be related to disease progression. In the moderate hepatic impairment cohort, 3 of the 5 cases of increased blood bilirubin levels were considered to be Grade 3 non-serious treatment unrelated AEs, and the remaining 2 cases were considered to be Grade 4 SUSARs. All of the 5 patients in the moderate hepatic impairment cohort with Grade 3 or 4 increased blood bilirubin levels had liver metastases. No patients in the mild hepatic impairment cohort experienced Grade 3 or 4 increased blood bilirubin levels.

12.1.2.15. Evaluator's overall conclusions on the hepatic impairment study

The PK data for TAS-102 in patients with mild hepatic impairment are considered to be satisfactory. Steady state systemic exposure (based on AUC_{tau}) for FTD was 18% lower in the mild hepatic impairment cohort compared to the normal hepatic function cohort, while steady state systemic exposure (based on AUC_{tau}) for TPI was almost identical for the two treatment cohorts. Steady state peak exposure (based on C_{max}) for FTD was 13% lower in the mild hepatic impairment cohort compared to the normal hepatic function group, while steady state peak exposure (based on C_{max}) for TPI was almost identical for the two treatment cohorts. The Cycle 1, Day 1 results for peak exposure (based on C_{max}) and systemic exposure (based on $AUC_{0\text{-}inf}$) for FTD and TPI in the mild hepatic impairment group relative to the normal hepatic function group do not give rise to concern. Overall, the PK results suggest that no adjustment to TAS-102 dosage is required for patients with mild hepatic impairment.

The PK data for TAS-102 in patients with moderate hepatic impairment are more problematic. The steady state PK data in patients with moderate hepatic impairment were based on 3 patients, while the single-dose PK data were based on 4 to 5 patients. The sample size for PK analysis in patients with moderate hepatic impairment was smaller than that planned for the study (that is, at least 6 patients with evaluable PK data). The small sample size for patients with moderate hepatic impairment makes meaningful interpretation of the exposure data difficult in this patient cohort. Both the geometric mean steady state systemic exposure (based on AUC_{tau}) and peak exposure (based on C_{max}) for FTD were not increased in patients with moderate hepatic impairment compared to patients with normal hepatic function, but both geometric mean steady state systemic exposure (based on AUCtau) and peak exposure (based on Cmax) for TPI were increased by 46% and 45%, respectively, compared to patients with normal hepatic function. There were no PK data in patients with severe hepatic impairment.

Overall, the safety data for patients with normal hepatic function and patients with hepatic impairment (mild; moderate) in the dedicated hepatic impairment study were consistent with the safety data from the pivotal efficacy and safety study (RECOURSE). However, the dedicated hepatic impairment study was stopped prematurely because of reports of Grade 3 or 4 increased blood bilirubin levels in 5 (83.3%) of the 6 patients in the moderate hepatic impairment cohort. Of the 5 patients in the moderate hepatic impairment cohort with increased bilirubin levels, 2 patients had Grade 4 events, which were considered to be SUSARs related to treatment with TAS-102, and 3 patients had non-serious Grade 3 events considered to be unrelated to treatment with TAS-102. Of the 5 patients, 2 had rectal cancer, 2 had colon cancer and 1 had biliary tract cancer. All 5 patients had liver metastases. The high incidence of increased bilirubin levels in patients with moderate hepatic impairment treated with TAS-102 suggests that patients with moderate or severe hepatic impairment should not be treated with the drug.

Grade 3 or 4 increased blood bilirubin levels were also reported in 2 (25%) of the 8 patients with normal hepatic function, comprising 1 patient with prostate cancer and liver metastases and 1 patient with pancreatic cancer and lung metastases at the start of the study. Therefore, in the 2

patients with normal hepatic function at baseline who developed Grade 3 or 4 increased bilirubin levels during treatment, liver metastases (with probable biliary obstruction) were a likely contributing factor. In both cases, the investigator reported progressive disease as the cause of study discontinuation and blood bilirubin elevation was assessed as not related to TAS-102. None of the 10 patients in the mild hepatic impairment cohort had Grade 3 or 4 increased bilirubin levels.

In summary, it is considered that the PK data from the dedicated hepatic impairment study suggest that no TAS-102 dosage adjustment is required for patients with mild hepatic impairment. However, the PK data for patients with moderate hepatic impairment are considered too limited to make meaningful recommendations relating to dosing. Furthermore, the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment is of concern and suggests that treatment with TAS-102 should not be undertaken in this patient population. There are no PK data on patients with severe hepatic impairment.

12.1.3. Question 2

TPI is metabolised primarily to 6-hydroxymethyl uracil (6-HMU). Please identify the sites and mechanisms involved in this transformation.

12.1.3.1. Sponsor's response

In vitro metabolic study of [14C]-TPI using human and rat liver S9 was performed in order to determine if metabolism involving cytochrome P-450 (P-450) was involved in generating TPI metabolites (Study 99C42, Study Report NP34092). However, no metabolite was found during the investigation using liver S9 (+NADPH system). These findings indicate that TPI was not metabolised by cytochrome P-450 in the liver.

During the clinical development of TAS-102, a Phase I open label study was performed to evaluate the mass balance of orally administered FTD and TPI as components of TAS-102 in patients with advanced solid tumours, using a light tracer dose of [14C]-FTD or [14C]-TPI (Study TPU-TAS-102-108, Study Report NP34337). After oral administration of TAS-102 with [14C]-TPI, overall, on average, 76.8 % of the total radioactivity (TRA) dose was recovered, consisting of 27.0 % urinary excretion and 49.7 % faecal excretion. Based on the animal study in rats with [14C]-TPI (Study AE-2350-2G, Study Report NP34137), the biliary excretion of TPI and metabolites is expected to be negligible in human. Thus, the majority of the TRA that was recovered in the faeces suggests moderate gastrointestinal absorption of TPI. In urine, TPI was the major component (79.1 % of urine TRA) and 6-HMU was the major metabolite of TPI (14.0 % of urine TRA). Therefore, renal clearance seems to be the major TPI elimination pathway, which minimises the potential impact of an inhibitor of the enzyme involved in the metabolism of TPI to 6-HMU.

12.1.3.2. Evaluation of response

The sponsor's response did not state the mechanism of conversion of the transformation of TPI to 6-HMU, nor did it identify possible sites where the transformation might occur. Review of the mass balance study report (TPU-TAS-102-108) indicates that 6-HMU as been identified as a major metabolite in rats, whereas in a Japanese clinical study (Study J001-10040010) the concentration of this metabolite was at trace levels both in both plasma and urine. Furthermore, in vitro studies using human hepatocytes or liver microsomes revealed that TPI is sparingly metabolised in these biomaterials, suggesting poor hepatic metabolism of this compound in humans. However, in the mass balance study, the radiochromatograms of pooled samples suggested that plasma total radio-activity (TRA) consisted of 30.9% 6-HMU and 53.1% TPI, urine TRA consisted of 14.0% 6-HMU and 79.1% TPI, and fecal TRA consisted of 34.4% 6-HMU and 48.2% TPI. The sponsor comments that the relatively large proportion of 6-HMU in the mass balance study is due to the longer sample collection time (up to 1 week) compared to the Japanese clinical study. In the mass balance study, broad secondary peaks in 6-HMU were observed at both plasma and blood at time-points later than 48 hours. Furthermore, the metabolite appeared in plasma or in blood after disappearance of TPI, which suggests that 6-HMU was slowly produced via a metabolic pathway other than hepatic metabolism.

12.2. Safety

12.2.1. Question 1

In the pivotal study (RECOURSE), the total number of weeks of exposure was approximately 4-fold longer in the TAS-102 group than in the placebo group (6743 versus 1791 weeks respectively). No safety data could be identified in the study report comparing safety outcomes in the two treatment groups adjusted for duration of exposure. Please justify the absence of pivotal comparative safety data (RECOURSE) adjusted for duration of exposure.

12.2.1.1. Sponsor's response

The sponsor stated that in the clinical study report submitted for RECOURSE analysis of the safety data adjusted for duration of exposure was performed and presented for treatment-related AEs. The sponsor states that although these results were not detailed (in the study report), it was concluded in the safety part that:

> *'while there were several safety aspects that showed a higher frequency for TAS-102 compared to placebo, the total time on treatment was nearly 4 times greater in the TAS-102 group than in the placebo group (TAS-102: 6744 weeks, placebo: 1791 weeks), thereby rendering a greater probability to detect events on the TAS-102 treatment arm than on placebo'.*

Moreover, treatment-related AE incidence rates adjusted for drug exposure were presented as a part of the answer to the major objection question at D120 of the EMA.

The sponsor provided an analysis of treatment-related AEs occurring during RECOURSE summarised by frequency and incidence rate adjusted for duration of exposure (based on a 100 patient-years exposure rate). The sponsor provided a discussion on the differences between the two treatment groups (TAS-102 versus placebo) in the treatment-related incidence rates (unadjusted versus adjusted for duration of exposure) based on the data provided below.

Table 73: RECOURSE pivotal Phase III study; Treatment-related adverse events as reported by the Investigator (≥ 10% in the TAS-102 group considering adverse events with PT clinically similar); Frequency and exposure adjusted incidence rates (% Patient-Years (PY)), All grades and Grade ≥ 3 in the Safety Set (N = 798)

Treatment-related [1] Adverse Events (preferred term)	TAS-102 (N = 533)	Placebo (N = 265)	TAS-102 (PY = 171.0)	Placebo (PY = 55.3)
	Frequency (%)		Incidence rate % PY [2]	
	All grades /Grade ≥ 3			
Anaemia	31.5/12.2	4.5/1.9	98.2/38.0	21.7/9.0
Haemoglobin Decreased	0.6/0.4	0.0/0.0	1.8/1.2	0.0/0.0
Neutropenia	28.7/20.1	0.0/0.0	89.5/62.6	0.0/0.0
Neutrophil count decreased	27.2/15.6	0.4/0	84.8/48.5	1.8/0.0
Thrombocytopenia	5.6/1.7	0.4/0.4	17.5/5.3	1.8/1.8
Platelet count decreased	14.4/2.4	1.5/0	45.0/7.6	7.2/0.0
Leukopenia	4.7/2.1	0.0/0.0	14.6/6.4	0.0/0.0
White blood cell count decreased	26.3/9.8	0.4/0	81.9/30.4	1.8/0.0
Nausea	39.4/0.9	10.9/0.0	122.8/2.9	52.4/0.0
Diarrhoea	23.6/2.3	9.1/0.0	73.7/7.0	43.4/0.0
Vomiting	20.1/0.6	4.5/0.0	62.6/1.8	21.7/0.0
Fatigue	24.8/2.1	10.2/1.9	77.2/6.4	48.8/9.0
Asthenia	10.9/1.7	4.5/0.8	33.9/5.3	21.7/3.6
Decreased appetite	26.5/1.7	11.3/0	82.5/5.3	54.2/0.0

N: total number of patients; Patient-Years (PY) = Total days of safety exposure (first dose through last dose + 30 days) from all patients in the group combined divided by 365.25; a. Treatment-related AEs in different SOC but corresponding to the same medical concept were also presented, that is, neutrophil and neutrophil count decreased; b. Incidence rates adjusted on drug exposure calculated as Patients/100 patient-Years.

12.2.1.2. Evaluation of response

The sponsor's response is satisfactory. The results discussed in this section are derived from the study report for RECOURSE. In RECOURSE, treatment-related AEs (any) adjusted for 100 patient years of exposure were reported with a similar incidence in the TAS-102 and placebo groups (267.3/100PY versus 262.2/100PY, respectively), while the incidence of ≥ Grade 3 treatment-related AEs was higher in the TAS-102 group than in the placebo group (152.6/100PY versus 47.0/100PY, respectively).

Treatment-related ≥ Grade 3 AEs (preferred terms) reported with an incidence of ≥ 2 patients/100PY in the TAS-102 group and ≥ 2-fold higher in the TAS-102 group than in the placebo group in descending order of frequency in the TAS-102 group were neutropaenia (62.6 versus 0), neutrophil count decreased (48.5 versus 0), anaemia (38.0 versus 9.0), white blood cell count decreased (30.4 versus 0), febrile neutropaenia (11.7 versus 0), platelet count decreased (7.6 versus 0), diarrhoea (7.0 versus 0), leukopaenia (6.4 versus 0), thrombocytopaenia (5.3 versus 1.8), decreased appetite (5.3 versus 0), lymphocyte count decreased (4.7 versus 1.8), and nausea (2.9 versus 0). There were no treatment-related ≥ Grade 3 AEs (preferred terms) reported with an incidence of ≥ 2 patients/100PY in the placebo group and ≥ 2-fold higher in the placebo group than in the TAS-102 group.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new efficacy data were submitted with the sponsor's post-first round response. Accordingly, the benefits of trifluridine/tipiracil (LONSURF) are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

After consideration of the safety data submitted with the sponsor's post-first round response, the risks of treatment with trifluridine/tipiracil (Lonsurf) remain substantially unchanged from those identified in the first round evaluation. However, based on the results of the dedicated hepatic impairment study submitted with the response it is recommended that Lonsurf should not be used to treat patients with moderate or severe hepatic impairment. The single- and multiple-dose PK data for FTD suggested that exposure to this component of TAS-102 in patients with moderate hepatic impairment was comparable to exposure in patients with normal hepatic function. However, the single- and multiple-dose PK data for TPI suggested increased exposure to this component of TAS-102 in patients with moderate hepatic impairment compared to patients with normal hepatic function. The PK exposure data for patients with moderate hepatic impairment should be interpreted cautiously due to the small number of patients in this patient population. Overall, it is considered that the PK data in patients with moderate hepatic impairment are too limited to allow clinically meaningful conclusions on dosage to be made for this patient population. Furthermore, the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment observed in the study raises concerns about the safety of Lonsurf in this patient population. The study supports the use of Lonsurf in patients with mild hepatic impairment without dose adjustment.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance for trifluridine/tipiracil (Lonsurf) given the proposed usage remains favourable for the reasons identified in the first round evaluation.

14. Second round recommendation regarding authorisation

It is recommended that trifluridine/tipiracil (LONSURF) be 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.

15. References

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