25 February 2016
EMA/CHMP/287846/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lonsurf

International non-proprietary name: **trifluridine / tipiracil**

Procedure No. EMEA/H/C/003897/0000

Note

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

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List of abbreviations

AE: Adverse event

ASMF: Active Substance Master File = Drug Master File

AT: As-treated (population)

AUC: Area under the curve

BCS: Biopharmaceutics Classification System

BID: Twice daily

BSA: Body surface area

BSC: Best supportive care

CI: Confidence interval

CL/F: Oral clearance

C_{max}: 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

DNA: Deoxyribonucleic acid

DPD: Dihydropyridine dehydrogenase

DR: Duration of response

EC: European Commission

ECG: Electrocardiogram

ECOG: Eastern Cooperative Oncology Group

eCRF: Electronic case report form

EGFR: Epidermal growth factor receptor

EMA: European medicines agency

EP: European Pharmacopoeia

EU: European Union

FAS: Full analysis set

FDA: Food and Drug Administration

FTD: Trifluridine

FTY: 5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione

GC: Gas Chromatography

GCP: Good clinical practice

G-CSF: Granulocyte colony-stimulating factor

HDPE: High Density Polyethylene

HPLC: High performance liquid chromatography

HR: Hazard ratio

ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IPC: In-process control

ITT: Intent-to-treat

LC/MS/MS: Liquid chromatography-tandem mass spectrometry

LDPE: Low density polyethylene

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

Ph. Eur.: European Pharmacopoeia

PK: Pharmacokinetics

PS: Performance status

QC: Quality Control

QD: Once daily

QTc: QT interval corrected for heart rate

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 Tumors

RH: Relative Humidity

SAE: Serious adverse event

SmPC Summary of Product Characteristics

SOC: System organ class

TID: Three times daily

$T_{1/2}$: Terminal elimination half-life

TK1: Thymidine kinase 1

T_{max}: Time of maximum observed plasma concentration

Tpase: Thymidine phosphorylase

TPI: Tipiracil hydrochloride

TR: Tumour response (evaluable population)

TTF: Time to treatment failure

UV: Ultraviolet

VEGF: Vascular endothelial growth factor

WBC: White blood cell

XRD: X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Taiho Pharma Europe Ltd. submitted on 27 February 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lonsurf, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 November 2013. On 19 October 2015, the marketing authorisation application was transferred to Les Laboratoires Servier.

The applicant applied for the following indication.

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tipiracil was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance tipiracil (as hydrochloride) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

Not applicable.

Licensing status

Lonsurf has been given a Marketing Authorisation in Japan on 24 March 2014 and United States on 22 September 2015.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Arantxa Sancho-Lopez

- The application was received by the EMA on 27 February 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2015.
- PRAC Rapporteur's Assessment Report was circulated on 23 June 2015.
- PRAC Rapporteur's Assessment Report was endorsed by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 October 2015, which included the request for transfer of the marketing authorisation application to Les Laboratoires Servier.
- PRAC Rapporteur's Assessment Report was circulated on 18 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 November 2015.
- PRAC Advice was adopted on 3 December 2015.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 January 2016.
- Updated PRAC Rapporteur's Assessment Report circulated 1 February 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 February 2016.
- PRAC Rapporteur's Assessment Report was endorsed by PRAC on 11 February 2016.
- During the meeting on 25 February 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lonsurf.

2. Scientific discussion

2.1. Introduction

Problem statement

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (Globocan 2012). In Europe, CRC is the most frequently diagnosed cancer and the second leading cause of cancer death. CRC was responsible for 215 000 deaths in Europe in 2012. The stage of disease at the time of diagnosis represents the most relevant prognostic factor. Five-year survival rates range from 93% for stage I disease to less than 10% for stage IV[1].

Surgery, followed by adjuvant chemotherapy in certain cases, represents the standard therapeutic approach for patients with loco-regional disease. However, approximately 25% of patients present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC. The CRC-related 5-year survival rate approaches 60%[2].

At present, there is no curative treatment for patients with mCRC. When left untreated, patients have a poor prognosis, with a median survival of about 6 months. With the exception of few selected patients where resection of metastases is indicated, the standard treatment for patients with metastatic disease is represented by systemic chemotherapy, which has demonstrated to significantly improve overall survival to an average of 20 months. The currently available systemic chemotherapeutic options for patients with mCRC consist essentially of fluoropyrimidine based regimens alone or in combination with oxaliplatin (FOLFOX, CAPOX) or irinotecan (FOLFIRI, CAPIRI). Fluoropyrimidine based regimens have demonstrated similar activity when given as first or second line therapy. Addition of the anti-VEGF monoclonal antibody bevacizumab to the above mentioned first or second line chemotherapies has been approved. In patients with RAS wild-type mCRC, the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab or panitumumab can also be administered as monotherapy or in combination with fluoropyrimidine-based regimens.

Aflibercept has been registered in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and the tumour microenvironment (PDGFR, FGFR). Regorafenib was approved for the treatment of patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.

[1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.
[2] Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(suppl 3): iii1-iii9.

About the product

TAS-102 (trifluridine/tipiracil, Lonsurf) 15 and 20 mg tablets, is a new antineoplastic agent. Lonsurf is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471).

Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, tipiracil hydrochloride. In nonclinical studies, trifluridine/tipiracil hydrochloride demonstrated antitumour activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of trifluridine/tipiracil hydrochloride against several human tumour xenografts correlated highly with the amount of trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.

The applicant applied for the following indication:

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

The recommended indication is:

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

The recommended starting dose of Lonsurf 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 (see section 4.4).

The dosage is calculated according to body surface area (BSA). The dosage must be rounded to the nearest 5 mg increment. The dosage must not exceed 80 mg/dose. If doses were missed or held, the patient must not make up for missed doses.

Table 1: Starting dose calculation according to body surface area (BSA)

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

Recommended dose adjustments

Dosing adjustments may be required based on individual safety and tolerability.

A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.

In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in Table 2, Table 3 and Table 4.

Table 2: Dose interruption and resumption criteria for haematological toxicities related to myelosuppression

Parameter	Interruption criteria	Resumption criteria[a]
Neutrophils	$< 0.5 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Platelets	$< 50 \times 10^9$/L	$\geq 75 \times 10^9$/L

[a] Resumption criteria applied to the start of the next cycle for all patients regardless of whether or not the interruption criteria were met.

Table 3: Recommended dose modifications for Lonsurf in case of haematological and non-haematological adverse reactions

Adverse reaction	Recommended dose modifications
• Febrile neutropenia • CTCAE* Grade 4 neutropenia ($< 0.5 \times 10^9$/L) or thrombocytopenia ($< 25 \times 10^9$/L) that results in more than 1 week's delay in start of next cycle • CTCAE* non-hematologic Grade 3 or Grade 4 adverse reaction; except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrheal medicinal products	• Interrupt dosing until toxicity resolves to Grade 1 or baseline. • When resuming dosing, decrease the dose level by 5 mg/m^2/dose from the previous dose level (Table 4). • Dose reductions are permitted to a minimum dose of 20 mg/m^2/dose twice daily. • Do not increase dose after it has been reduced.

* Common terminology criteria for adverse events

Table 4: Dose reductions according to body surface area (BSA)

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg	20 mg	
Level 1 dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	2	0	60
	1.09 - 1.24	35	1	1	70
	1.25 - 1.39	40	0	2	80
	1.40 - 1.54	45	3	0	90
	1.55 - 1.69	50	2	1	100
	1.70 - 1.94	55	1	2	110
	1.95 - 2.09	60	0	3	120
	2.10 - 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	2[a]	1[a]	50[a]
	1.10 - 1.29	30	2	0	60
	1.30 - 1.49	35	1	1	70

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg	20 mg	
	1.50 - 1.69	40	0	2	80
	1.70 - 1.89	45	3	0	90
	1.90 - 2.09	50	2	1	100
	2.10 - 2.29	55	1	2	110
	≥ 2.30	60	0	3	120
Level 3 dose reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	0	1	40
	1.14 – 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

[a] At a total daily dose of 50 mg, patients should take 1 x 20 mg tablet in the morning and 2 x 15 mg tablets in the evening.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 15 mg trifluridine and 6.14 mg tipiracil (as hydrochloride) or 20 mg trifluridine and 8.19 mg tipiracil (as hydrochloride) as active substances.

Other ingredients are:

Tablet core: lactose monohydrate, pregelatinized maize starch, stearic acid

Film coating:

Lonsurf 15 mg/ 6.14 mg film-coated tablets
hypromellose, macrogol (8000), titanium dioxide (E171), magnesium stearate

Lonsurf 20 mg/ 8.19 mg film-coated tablets
Hypromellose, macrogol (8000), titanium dioxide (E171), iron oxide red (E172), magnesium stearate

Printing ink: shellac, iron oxide red (E172), iron oxide yellow (E172), titanium dioxide (E171), indigo carmine aluminium lake (E132), carnauba wax, talc

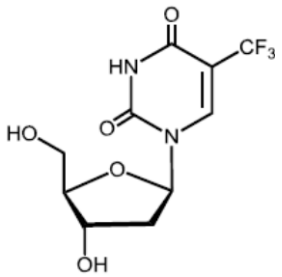
The product is available in aluminium/aluminium blister with laminated desiccant (calcium oxide) as described in section 6.5 of the SmPC.

2.2.2. Active substance

Trifluridine

General information

The chemical name of trifluridine is 2'-deoxy-5-(trifluoromethyl)uridine corresponding to the molecular formula $C_{10}H_{11}F_3N_2O_5$. It has a relative molecular mass of 296.20 g/mol and the following structure:



The active substance is a non-hygroscopic white crystalline powder soluble in water and buffer solution at pH 2-12.

Trifluridine exhibits stereoisomerism due to the presence of 3 chiral centres in the sugar moiety. Stereoisomerism is controlled by starting material specifications and process reaction conditions. In addition, enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for active substance. The chosen crystal form is consistently manufactured and remains stable on storage of the active substance.

Manufacture, characterisation and process controls

The active substance is synthesized by one manufacturer in seven main steps using commercially available well defined starting materials with acceptable specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The following techniques were used in the study of the structure of trifluridine: elemental analysis, infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, UV-visible spectrophotometry and X-ray analysis of crystal structure. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double LDPE bags inserted into a HDPE drum. The LDPE bags comply with Regulation EC 10/2011 as amended

Specification

The active substance specification includes tests for: description, identity (IR, HPLC), specific optical rotation (Ph. Eur.), heavy metals (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), and residue on ignition (Ph. Eur.), microbial contamination (Ph. Eur.).

The absence of a control for polymorphism in the specification is considered justified. Data have been presented showing that the manufacturing process consistently produces the same crystal form of trifluridine. The polymorphic form has also been controlled in the stability studies. The absence of particle size control is justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions at 25 ºC / 60% RH (6 batches) and for 6 months under accelerated conditions at 40 ºC / 75% RH (3 batches) according to the ICH guidelines.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Results on stress conditions (40°C/75%RH/3 months, 60 °C/3 months, purified water/80°C/2 hours, 0.1 mol/L Hydrochloride acid/80°C/2 hours, 0.1 mol/L sodium hydroxide solution/ambient temperature/3hours, hydrogen peroxide 15%/5°C/19 hours) were also provide on one batch.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. Additionally, polymorphic form was tested by XRPD as well as identification by fluoride and UV tests.

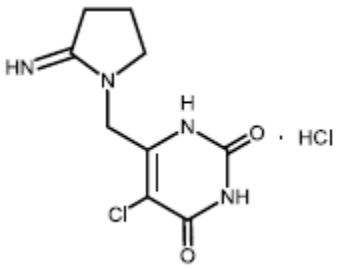
No significant change was observed in the long term and accelerated conditions. For the stress testing in the solid state, no significant changes related to related substances were observed. The active substance was stable under high temperature at 60°C, high humidity at 40°C/75%RH and exposure to light. Based on the stability results of stress conditions (purified water/80°C/2 hours, 0.1 mol/L Hydrochloride acid/80°C/2 hours, 0.1 mol/L sodium hydroxide solution/ambient temperature/3hours, hydrogen peroxide 15%/5°C/19 hours), potential degradation pathway were established.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container.

Tipiracil hydrochloride

General information

The chemical name of tipiracil hydrochloride is 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride corresponding to the molecular formula $C_9H_{11}ClN_4O_2$ HCl. It has a relative molecular mass of 279.12 g/mol and the following structure:



The active substance is a non-hygroscopic white crystalline powder freely soluble in water and buffer solution at pH 1-12.

The active substance has a non-chiral molecular structure. Polymorphism has been observed. The more thermodynamically stable crystal form, is produced consistently in the manufacturing process. Polymorphic form control has been included in the active substance specification.

Manufacture, characterisation and process controls

The active substance is synthesized by one manufacturer in three main steps using commercially available well defined starting materials with acceptable specifications.
Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. The structure of tipiracil was investigated using the following techniques: elemental analysis, mass spectrometry, ultraviolet-visible spectrophotometry, infrared spectrophotometry, nuclear magnetic resonance spectroscopy and X-ray analysis of crystal structure. Potential and actual impurities were well discussed with regards to their origin and characterised.

Changes introduced during manufacturing process development have been presented in sufficient detail and have been justified.

The active substance is packaged in double polyethylene bags in fiber drum. The polyethylene bags comply with EC 10/2011 Regulation as amended.

Specification

The active substance specification includes tests for: description, identity (IR, HPLC, XRD), identification chloride, heavy metals (Ph. Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Ph. Eur.), and residue on ignition (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided for several batches including four production scale batches of the active substance. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on three pilot scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for 36 months under long term conditions at 25 ºC / 60% RH and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

Photostability testing was performed on one batch with conditions similar to the ICH guideline Q1B conditions. Results on stress conditions (40°C/75%RH/3 months, 60 °C/3 months, purified water/80°C/3 hours, 0.1 mol/L Hydrochloride acid/80°C/4 hours, 0.1 mol/L sodium hydroxide solution/ambient temperature/0.5 hours, hydrogen peroxide 30%/room temperature/24hours) were also provide on one batch.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. In addition, microbiological purity, clarity and colour of solution and pH were studied.

No significant change was observed in the long term and accelerated conditions. Results of photostability study showed that the active substance is not light sensitive. Based on the stability results of stress conditions potential degradation pathways were established

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Trifluridine/Tiparacil Hydrochloride (FTD/TPI) is an immediate release film-coated tablet. The different tablet strengths are appropriately differentiated by their colour and imprinting as follows:

15/7.065 mg film-coated tablets are white, round, biconvex, imprinted with "15" on one side, and "102" and "15 mg" on the other side, in gray ink. The tablets have a diameter of approximately 7.1 mm and a thickness of approximately 2.7 mm.

20/9.420 mg film-coated tablets are pale red, round, biconvex, imprinted with "20" on one side and "102" and "20 mg" on the other side in gray ink. The tablets have a diameter of approximately 7.6 mm and a thickness of approximately 3.2 mm.

Both active substances are BCS class III compounds. The influence of the particle size distribution of both active substances on the content uniformity of tablets, the dissolution profile and the tablet hardness was studied. Based on the study results the particle size of FTD was not considered to be critical. Regarding TPI, the results indicated that particle size distribution of this API has an impact on the content uniformity of tablets.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The colorants used comply with EU regulation 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The choice of the excipients has been satisfactorily justified and their levels have been chosen based on formulation optimisation studies. The compatibility of the active substance with the excipients and the compatibility of active substance with each other have been adequately demonstrated.

Both formulations (15/7.065 mg and 20/9.420 mg tablets) are dose proportionate.

For the finished product, the base formulation used in clinical studies for other clinical indications formed the starting point for the development of tablets for the proposed indication. Using this base formulation, an early clinical trial formulation was developed in order to optimize the manufacturing method. The process employed to produce the base formulation was chosen in view of excipient compatibility results. Lactose monohydrate as a diluent, carmellose as a disintegrant and stearic acid as a lubricant were selected as the excipients based on compatibility test results for the base formulation. In addition, a film coating was applied to prevent any hazard due to dusting of high potency active substances. Because carmellose in the base formulation was not a compendial article in Europe or the US at the time of development, to facilitate regulatory approval, the disintegrant was changed from non-compendial carmellose to compendial pregelatinized starch. Furthermore there was a concern regarding exposure to the active ingredients during manufacturing. Thus, the manufacturing method was changed to a direct compression method that is simpler and causes less dusting and minimizes exposure to the active ingredients. Associated with the change in the manufacturing method, a different type of lactose monohydrate was used as the diluent. After that, minor changes were made (e.g. for both strength magnesium stearate was added; for the 20 mg strength, the shape of the tablet was changed and red ferric oxide was added) to develop the late clinical trial formulation used in the Phase III clinical study. The compositions of the phase III clinical batches are the same as the to-be marketed formulation, with the exception regarding the imprinting on the tablet surface. The manufacturing process is the same with the difference of the batch scale (four-fold increase), and the manufacturing site.

The comparative dissolution profiles of phase I/II formulation vs phase III formulation using the Quality Control (QC) method and the following medium: water, buffered media at pH 1.2/4.5/6.8, FaSSIF (fasted state simulated intestinal fluid, pH 6.5) and FeSSIF (fed state simulated intestinal fluid, pH 5.0) showed that the differences between phase I/II formulation and phase III formulation do not affect dissolution. To provide further assurance that phase I/II formulation and phase III formulation are comparable, a bioavailability study was performed using the highest dose strength tablets (20 mg). It was concluded that the differences in the formulation and tablet shape had no influence on in vivo absorption.

The comparative dissolution profiles of phase III formulation vs proposed formulation using the QC method and the QC medium (0.1 N HCl) showed that the differences between phase III formulation and the proposed formulation do not affect dissolution.

The discriminatory power of the dissolution method has been demonstrated.

FTD/TPI film-coated tablets are manufactured by a standard compression process. The studies performed demonstrated that the manufacturing process posed no risk to content uniformity.

The primary packaging is aluminium/aluminium blister with laminated desiccant (calcium oxide). The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: milling of the two active substances, mixing of the raw materials, tableting and film-coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three production scale batches per tablet strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The critical steps have been identified .The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Information about the storage and transportation of the bulk tablet are provided. The maximum holding time for the bulk tablets is validated.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form : description, identification (HPLC, UV), dissolution (HPLC, Ph. Eur.), uniformity of dosage units (Ph. Eur.), elemental impurities (Ph. Eur.), related substances (HPLC), assay (HPLC), water content (Ph. Eur.), and microbial test (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for several development batches including clinical batches and for three production scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for three production scale batches of each strength stored under long term conditions for 18 months at 25 ºC / 60% RH and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to shelf-life specifications described in the section above. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

No significant changes have been observed in the long term and accelerated stability studies. Photostability results demonstrated that the product is not light sensitive.

To support the storage and shipment of bulk tablets to the packaging site, the following studies have been performed: bulk stability studies, thermal cycle study (-20°C - 40°C/75% RH), bulk shipping studies. No significant changes have been observed.

Based on available stability data, the proposed shelf-life of 30 months with no special storage precaution as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

The magnesium stearate and stearic acid are of vegetable origin.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

TAS-102 has undergone a series of nonclinical studies to support its use in adult patients with metastatic colorectal cancer who have been previously treated with, or are not candidates for, standard chemotherapies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

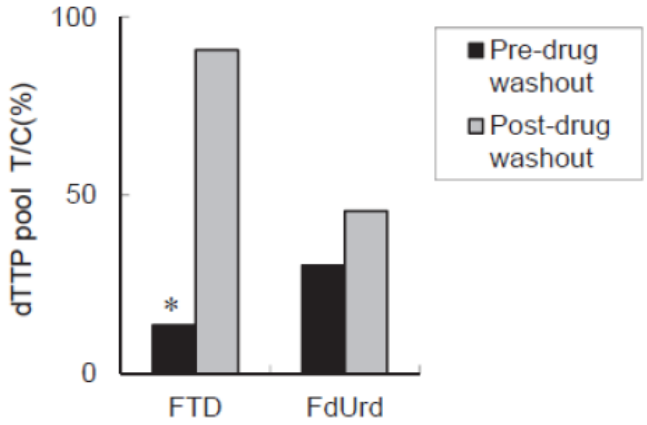
In vitro studies

The IC50 values of FTD and 5-Fu for inhibition of cultured human cancer cell line investigated in study 20061-004, were in a similar range, varying from 0.214-24.4 µM for FTD and from 3.18-17.7 µM for 5-FU. However, the IC50s against cell lines DU145 and CCRF-CEM differed markedly between FTD (1.48 and 0.214 µM) and 5-FU (7.70 and 8.40 µM).

Table 10: Influence of FTD and 5-FU (IC_{50} µM) on the proliferation of human cancer cell lines *in vitro*

		IC_{50} (µM)	
Cell Line	**Origin**	**FTD**	**5-FU**
NUGC-3	Gastric carcinoma	3.46	8.50
HCT-15	Colorectal carcinoma	10.7	4.96
A549	Lung carcinoma	3.50	3.18
MDA-MB-435	Breast carcinoma	14.4	4.39
SK-OV-3	Ovarian carcinoma	24.4	14.0
HeLa	Uterine carcinoma	8.15	9.12
J82	Bladder carcinoma	8.66	9.15
DU145	Prostatic carcinoma	1.48	7.70
CFPAC-1	Pancreatic carcinoma	2.05	3.25
KB	Head/neck carcinoma	5.84	17.7
CCRF-CEM	Leukemia	0.214	8.40

In a study investigating the sustainability of inhibitory effect of FTD on TS by measurement of intracellular dTTP pool in HeLa cells (study 20111-003), the dTTP pool was reduced during exposure to both FTD and FdUrd, but the dTTP pool following drug washout recovered markedly better with FTD than with FdUrd. TS inhibitory action was cancelled more quickly following drug washout with FTD than with FdUrd.



DRUG	dTTP pool T/C (%)	
	Pre-drug washout	Post-drug washout
FTD	13.6	90.7
FdUrd	30.3	45.5

Figure 4: Influence of FTD or FdUrd on the dTTP pool (T/C%) after 4 h incubation (Pre-drug washout) and following 4 h washout (Post-drug washout) n=3

Upon uptake of FTD in NUGC-3 and MCF-7 cells, the amount of FTD uptake into DNA was much greater than that of the other nucleosides, Ara-C, dFdC and FdUrd (study M01-2006-0025).

In vivo studies

The antitumor efficacy of oral administration (twice daily) and continuous infusion (osmotic pump) of FTD for 14 days in MX-1 human breast cancer xenografted nude mice was evaluated in study 11TA03. Approximately one month after inoculation, 2 mm fragments of tumour were excised and subcutaneously implanted into the right chest of male BALB/cAJclnu/ nu mice. Groups were formed such that mean tumour volume (TV) between groups was equal. Then administration with either TAS-102 or its anti-tumour component FTD or a comparator followed for 14 or 28 days. Relative tumour volume (RTV) was calculated from each calculated tumour volume (TV) calculated on certain days (n) The inhibition rate of tumour growth (IR) was calculated from the RTV most often at Day 15. RTV and IR were calculated using the following formulas: RTVn = (TV on Day n) / (TV on Day 0) and IR (%) = [1-(mean RTV15 of treatment group) / (mean RTV15 of control group)] × 100. As indicator for toxicity, changes in body weight (reductions of >20 %) were taken.

A comparison of the RTV between the oral administration group and the continuous infusion group showed that oral administration resulted in significantly higher anti-tumour efficacy ($p<0.01$). Oral administration of FTD seems to be superior to continuous infusion, confirming the validity of oral administration

The anti-tumour efficacy between once daily and twice daily oral administration of TAS-102 for 14 days in MX-1 human breast cancer xenografted nude mice was evaluated in study 11TA04 . The anti-tumour efficacy of TAS-102 is higher when the compound is given as a divided daily dose compared to a single dose in human breast tumour MX-1 xenografts in nude mice, suggesting that administration of TAS-102 using a divided-dosing regimen may result in greater efficacy.

The effective dose levels of TAS-102 that could be administered to substantially reduce the growth of human gastric carcinoma SC-2 xenografts in nude mice were determined in study 20061-003. Tumour volume reduction following treatment with TAS-102 (500 mg/kg/day) was associated with significant toxicity (23.5%

weight loss) at Day 15. In comparison, weight loss following treatment with 250 mg/kg/day was circa 5%, suggesting that the optimum dose level of TAS-102 against SC-2 human gastric cancer xenografts in nude mice lies between 250 and 500 mg/kg/day.

In nude mice bearing intraperitoneally implanted human colon adenocarcinoma (KM20C) tumours, TAS-102 showed superior prolongation of survival compared with CPT-11 and S-1-treated mice (28 days) bearing human colon adenocarcinoma (KM20C) xenografts (study 11TA05). These findings suggest that TAS-102 may be effective in prolonging survival of advanced and recurrent colorectal cancer in patients.

In mice bearing human colon cancer (KM20C), human breast cancer (MC-2) and human lung cancer (Lu-134) xenografts, treatment with TAS-102 (150 mg/kg/day, b.i.d.) for 14 consecutive days, showed significant ($p < 0.01$) anti-tumour activity against all three tested human cancer xenografts in nude mice (study 03-09-008). TP expression was observed in KM20C, MC-2, and Lu-134 tumours, with the highest expression in MC-2 tumours.

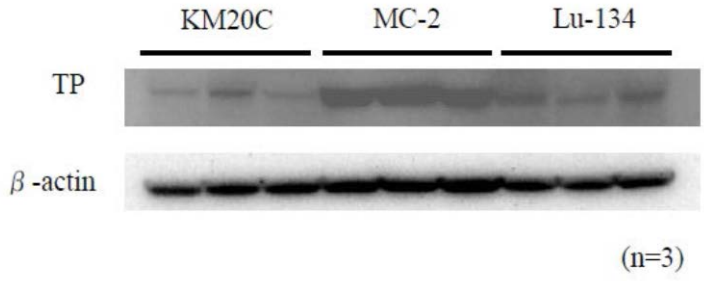


Figure 5: Expression levels of TP in human KM20C, MC-2 or Lu-134 tumor cells (all n=3/group)

However, whilst TP was expressed in all three tumour types investigated, TPI showed no anti-tumour efficacy in this study, suggesting that TPI acts solely as a modulator to inhibit the degradation of FTD (the TAS-102 effector) in blood, with little or no direct involvement in the anti-tumour efficacy of TAS-102. MC-2 and Lu-134 human xenografts in nude mice seem to be more effectively inhibited by TAS-102 in comparison to KM20C human xenograft.

The anti-tumour effect of TAS- 102 on the human colon cancer-derived cell line COL-1 and the mutant KRAS-containing cell line HCT-116 was evaluated in nude mice bearing subcutaneously implanted tumours (study 11TA01). TAS-102 is more effective than cetuximab on cetuximab insensitive colorectal cancer xenograft in nude mice, which may suggest that TAS-102 will be effective in treating patients with progressive, recurrent colorectal cancer and KRAS mutations that do not respond to cetuximab.

Table 11: Inhibition of COL-1 and HCT-116 human colon adenocarcinoma xenografts in nude mice by TAS-102 and cetuximab.

	COL-1 (wt KRAS)	HCT-116 (mutant KRAS)
Cetuximab, 40 mg/kg IP on day 1, 4, 8, 11	80.8 %	0.6 %
TAS-102, 150 mg/kg/day p.o. BID	55.8 %	55.5%

NB No toxicity-related deaths were recorded during the administration period of either drug.

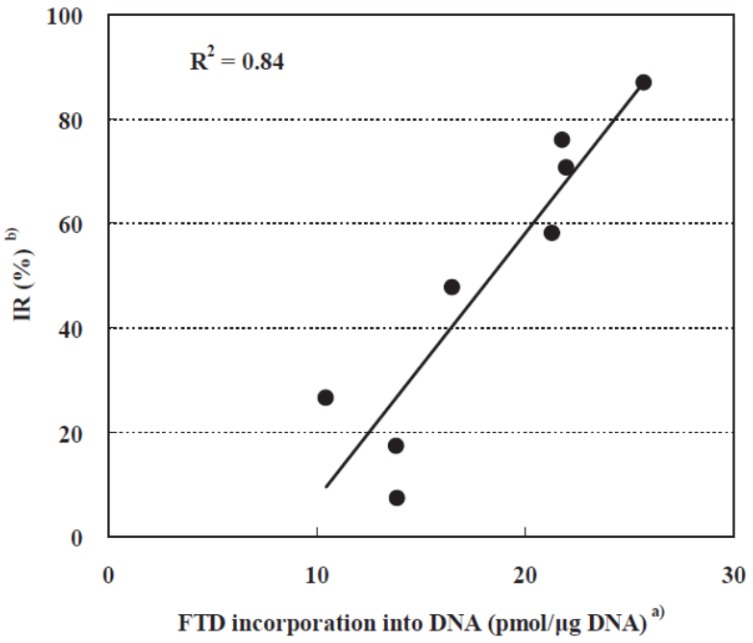
The anti-tumour activity of TAS-102 and TS-1 against MX-1 human breast cancer xenografts in nude mice was evaluated in study 11TA02. The IR of the TAS-102 (150 mg/kg/day) treated group was 64.3 % and of the TS-1 (8.3 mg/kg/day) treated group 10.5%. Compared to control, both TAS-102 and TS-1 produced significant

anti-tumour activity (RTV), which was significantly higher for TAS-102 over TS-1 against MX- 1 human breast cancer xenografts in this model.

A correlation analysis between the anti-tumour efficacy of TAS-102 in vivo and the amount of FTD incorporated into DNA was conducted (study 03-12-003). The high degree of association (R2 = 0.84) between the anti-tumour efficacy of TAS-102 and the amount of FTD incorporated into DNA confirms incorporation of FTD into DNA as the main effector mechanism for the anti-tumour activity of TAS-102.

Figure 6: Anti-tumor efficacy (IR%) of TAS-102 (Day 15) and FTD incorporation into DNA (pmol/ μ g DNA) on Day 7, in mice subcutaneously implanted with various human-derived tumour cell lines (table) and the correlation between these two (graph)

Human tumor cell line	Anti-tumor effect of TAS-102 (IR%)	FTD incorporation into DNA(pmol/µg DNA)
DLD-1	7.3	13.9
HT-29	17.2	13.8
SW480	26.4	10.4
HCT-116	47.6	16.5
MC-2	58.0	21.3
Lu-134	75.8	21.8
KM20C	70.5	22.0
MX-1	86.9	25.7



The mechanism(s) underlying the anti-tumour efficacy of TAS-102 were investigated by means of transcription analysis using mice bearing subcutaneously implanted KM20C human colon tumour xenografts (study

03-12-012). On the basis of a transcription study in cells from mice bearing KM20C tumour and treated with TAS-102, it is suggested that the decreased expression of genes under control of TBP observed following TAS-102 administration could be attributable to the incorporation of FTD into A-T-rich promoter regions, thus influencing the interactions between DNA and transcription factors

Which TBP regulated genes are expressed to a lesser extent in tumours inhibited by TAS-102 and how decrease in expression of these genes leads to tumour inhibition is not unravelled. This lack of information will not influence the benefit/risk balance of this product.

Secondary pharmacodynamic studies

The applicant has conducted receptor screening studies for FTD, FTY and TPI at concentrations of 10µM.

No significant interaction between FTD, TPI, FTY and different receptors, enzymes and channels tested has been reported up to the tested concentration of 10µM, which is in excess of the free maximum concentration of FTD, FTY and TPI in human serum upon dosing with Lonsurf according to the clinical dosing regimen. It can thus be anticipated that no secondary pharmacological effects will occur.

Table 12: calculation of the maximum plasma concentration in µM of FTD, FTY and TPI in humanplasma

Test compound	C_{max} ng/mL (plasma)	Molecular Weight (g/mol)	C_{max} µM (plasma)
FTD	4752 - 5448	296.20	18.39
FTY	560 -718* & 904**	180.08	5.02
TPI	69 - 79	279.12	0.28

* after multiple dosing
** after single dosing TPU-TAS-102-103

Safety pharmacology programme

Effects on CNS, respiratory and cardiovascular systems have been studied in rat and monkey for TAS-102, FTD and TPI. Effect of FTD and TPI on hERG current has been studied in HEK293T cells.

Oral administration of TAS-102 at dose levels of up to 435 mg/kg of FTD, or TPI at dose levels of up to 2000 mg/kg produced no treatment related behavioural, physiological, body temperature changes or respiratory parameters in the rat when compared to the vehicle treated group (studies B040836, B061097, B050588, B040837, B061098 and B050587).

Oral administration of TAS-102 at dose levels of up to 108.8 mg/kg of FTD and oral administration of TPI at dose levels of up to 1000 mg/kg produced no effects on cardiovascular parameters in the conscious monkey (studies B040835, B061099 and B050589).

The effect of FTD was assessed in vitro on the peak hERG tail current recorded from a HEK293 cell line stably expressing the hERG (human ether a go go related gene) potassium channel (studies B050268 or B050270). FTD is considered to have no effect on hERG current at concentrations up to 300 µmol/L (88.86 mg/L) and TPI is considered to have no effect on hERG current at concentrations up to 100 µmol/L (24.3 mg/L). Human Cmax for FTD is 4.8 mg/L and for TPI 0.068 mg/L.

Pharmacodynamic drug interactions

The inhibitory effects of FTD on cell proliferation when used concomitantly with dThd analog-type antiviral drugs in vitro were determined in study 03-13-004. None of the tested zidovudine (AZT), stavudine (d4T) or

telbivudine (LdT) influenced the inhibitory action of FTD on cell growth at clinically relevant concentration with HCT116 and NUGC-3 cancer cell lines. Zidovudine (AZT) attenuated the cell growth inhibitory effects of FTD, mainly at near clinical concentration of AZT. This would suggest that the possibility that the anti-tumour effects of Lonsurf could be attenuated when AZT is used concomitantly in clinical practice.

2.3.3. Pharmacokinetics

Single dose pharmacokinetics were studied in mice, rats and monkeys. Tissue distribution was studied in rats. Metabolism and excretion were studied in rats and monkeys.

Analytical methods

In toxicokinetic studies, FTD, FTY and TPI in plasma were measured by LC-MS/MS methods in rats, by HPLC-UV methods in dogs and by LC-MS/MS or HPLC-UV in monkeys. The methods were sufficiently validated.

FTD

Absorption

Based on excretion in urine and expired air and in rats also bile, at least 77% and 79% of FTD was absorbed in rat and monkey respectively. After oral administration, Tmax of FTD was similar among animal species (mouse 0.17 – 0.33 h, rat 0.25 – 0.5 h, monkey 0.9 – 1.5 h) and slightly longer in humans (1.3 – 2.1 h), indicating rapid absorption. FTD was rapidly metabolised into FTY (Tmax after oral administration mouse 0.33 – 2 h, rat 1 h, monkey 1.1 – 1.8 h, human 2.0 – 2.7 h). Absorption in humans appears much lower than in rats and monkeys, based on low excretion of FTD + metabolites in urine and low membrane permeability in Caco-2 cells.

Oral bioavailability of FTD (administered without TPI) was low (3.0% in monkeys) due to a high first-pass effect. The exposure to FTD (based on AUC(0-inf) increased 2.5 times in mice and 100 times in monkeys due to the co-administration with TPI. Molar ratios for FTD/TPI of 1:1 and 1:0.5 provided a significantly higher exposure to FTD in monkeys than a ratio of 1:0.2.

Elimination half-life of FTD was short, 0.21 h in rats and 0.22 h in monkeys following IV administration. In mice, conversion into FTY was too quick to determine a half-life for FTD. In humans, half-life was also short (1.4 – 1.7 h following oral administration).

Vd and CL were only provided for monkeys. CL/F was much higher for FTD alone (44.4 L/h/kg) than for FTD combined with TPI (0.35 L/h/kg), probably due to the fast conversion of FTD to FTY when FTD is administered without TPI. Vd/F for FTD alone (20.7 L/kg) was higher than total body water. Vd/F for FTD combined with TPI (0.585 L/kg) was lower than total body water.

Repeated dose plasma pharmacokinetics studies were not performed. Toxicokinetic studies showed no consistent gender effects in the exposure to FTD and FTY in rats and monkeys. Exposure to FTD increased approximately dose-proportionally at lower doses and less than dose-proportionally at higher doses in rats and monkeys. Exposure to FTD and FTY in rats showed some potential for accumulation following repeated dosing. In monkeys, no effect was observed from repeated dosing.

Distribution

Plasma protein binding of FTD was 83%, 72%, 45%, 91% and 97% in mouse, rat, dog, cynomolgus monkey and human. The high protein binding for humans compared to the animal species provides extra safety margins: factor 5.7 for the mouse, 9.3 for the rat, 18 for the dog, and 3.0 for the monkey at clinical concentrations.

In blood of rats, cynomolgus monkeys and humans, ^{14}C-FTD did not distribute to blood to a significant extent, at clinically relevant concentrations (blood/plasma ratios were around 0.6 – 0.8 in vitro and comparable or slightly higher in vivo).

^{14}C-FTD was found at the highest concentrations in large intestine, urine in bladder, uveal tract, bone marrow, and thymus. Low concentrations were found in the brain. The reliability of this study is however limited because measurements were started several hours after the plasma peak and because total radioactivity was measured, which at 4 h after dosing consisted mainly of FTY. There was no evidence of significant binding to melanin.

FTD and metabolites distributed to rat foetal tissues in substantial amounts. At 48 h after dosing, still substantial amounts remained. FTD (including metabolites) was excreted in milk of rats.

Metabolism

In vitro studies: FTD was not metabolized by human liver microsomes. FTD was metabolized into FTY (44.5-92.3% of the total radioactive peak area) and 5-CU (2.1-7.8% of total radioactive peak area) by cryopreserved human hepatocytes. 5-CdUrd was formed non-enzymatically (0.0-2.3% of total radioactive peak area). FTD was primarily metabolized by thymidine phosphorylase. Published in vitro data indicate that the metabolism of FTD into FTY s not inhibited by TPI in dogs.

In vivo studies: In rats, monkeys and humans FTY is the major metabolite. In plasma of rats, also a minor unknown metabolite was found. Urine excretion data in rats treated with radio-labelled TAS-102 vs radio-labelled FTD indicate that metabolism of FTD into FTY is inhibited by TPI in rats, though to a limited extent. In plasma of monkeys, also hydrolysed FTY and glucuronides of FTD were found, as well as other minor metabolites. In humans, 5-CU and 5-CdUrd are minor metabolites. These were not found in plasma of rats or monkeys. This is however not a problem, as they are only very minor metabolites in humans.

Excretion

Excretion of radioactivity following the oral administration of ^{14}C-FTD to non-fasted male rats in urine, faeces, expired air and bile was 61%, 21%, 16% and 0.4% respectively. Considering the low excretion in bile, excretion in faeces probably mainly consisted of unabsorbed dose. In cynomolgus monkeys, 79% of radioactivity was excreted in urine following the oral administration of ^{14}C-FTD. Excretion in faeces was 4%. Excretion was almost complete in 7 days. In humans, 1.5% of the administered dose of TAS-102 was excreted as unchanged FTD in urine and 21.0% of the administered dose was excreted as unchanged FTD + metabolites, which is much lower than in rats and monkeys. Excretion in faeces was not determined in humans.

TPI

Absorption

Based on excretion in urine and expired air and in rats also bile, approximately 15-24% and 27% of TPI was absorbed in rat and monkey respectively. In rats, absorption was 19% based on the ratio of AUCs of total radioactivity following oral and IV administration. After oral administration, Tmax of TPI was short in mice and rats (0.33 h and 0.5 – 1 h resp.) and slightly longer in monkeys and humans (2.3 h and 2.3 – 3.5 h resp.), indicating rapid absorption.

Bioavailability of TPI was low in rats (9%), probably mainly due to the low absorption.

Elimination half-life of TPI following IV administration was approximately 1.5 h in rats. Half-life following oral administration was 2.4 – 3.5 h in mouse and 1.8 h in monkey (no half-life after IV administration available in these species). This was similar to humans (1.7 – 2.2 h).

CL/F was higher in the mouse (73.3 – 73.7 L/h/kg) than in the monkey (2.14 L/h/kg). Vd/F was high in the mouse and far beyond total body water (258 – 372 L/kg). Vd/F in the monkey was 5.56 L/kg which was higher than total body water.

Toxicokinetic studies showed no consistent gender effect in rats except at the highest dose (2000 mg/kg/day) where exposure was higher in females. In monkeys, no consistent gender effect was visible after treatment with TAS-102. After administration of TPI alone (at higher doses than in the studies with TAS-102), exposure was lower in female monkeys than in males. Exposure to TPI increased approximately dose-proportionally in rats after administration of TAS-102 and less than dose-proportionally in the study with administration of TPI alone (at higher doses than in the studies with TAS-102). Exposure to TPI increased less than dose-proportionally in monkeys. There was no evidence of accumulation or induction of TPI in rats and monkeys.

Distribution

Plasma protein binding of TPI was low, 5.5%, 1.9%, 3.1%, 3.0% and 7.1% in mouse, rat, dog, cynomolgus monkey and human.

In blood of rats, cynomolgus monkeys and humans, ^{14}C-TPI did not distribute to blood to a significant extent, at clinically relevant concentrations (blood/plasma ratios were around 0.6 – 0.8 in vitro and comparable or slightly higher in vivo).

^{14}C-TPI was mainly found in large intestine, small intestine and liver. There was no distribution of TPI to the brain. The reliability of this study is however limited because measurements were started several hours after the plasma peak. There was no evidence of significant binding to melanin.

TPI and metabolites were distributed to rat fetal tissues in small quantities. TPI (including metabolites) was excreted in milk of rats.

Metabolism

In vitro studies: TPI was not metabolized by rat and human liver S9 or by cryopreserved human hepatocytes.

In vivo studies: 6-hydroxymethyluracil (6-HMU) was the main metabolite of TPI in rats. In monkeys, uracil was an important metabolite. The parent compound was also an important component in monkey plasma. There were also other metabolites in plasma of monkeys which were not further identified. In humans, no metabolites of TPI were found in plasma except that 6-HMU was found at very low amounts. 6-HMU was also found in rats. There are therefore no unique human metabolites of TPI.

Excretion

Excretion of radioactivity following the oral administration of ^{14}C-TPI to non-fasted male rats in urine, faeces, expired air and bile was 14-24%, 68-83%, 0.4% and 0.2% respectively. Considering the low excretion in bile, excretion in faeces probably mainly consisted of unabsorbed dose. Following the oral administration of ^{14}C-TPI to monkeys, 27% of radioactivity was excreted in urine and 68% in faeces. Excretion was complete in 7 days. In humans, approximately 29% of the administered dose of TPI was excreted in urine in its unchanged form, which is higher than in rats and monkeys. Excretion in faeces was not determined in humans.

FTD and TPI

Based on plasma pharmacokinetics and metabolism, rat and monkey are suitable animal species for the pivotal toxicology studies. Dog would have been a less suitable species because FTD metabolism is not inhibited by TPI in dogs.

Pharmacokinetic drug interactions

In vitro studies with human biomaterials showed no evidence that trifluridine, FTY and tipiracil are metabolized by the CYP enzymes tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). *In vitro* evaluation indicated that trifluridine and FTY had no inductive effect on human CYP1A2, CYP2B6 or CYP3A4/5 suggesting that neither trifluridine, FTY, nor tipiracil would cause, or be affected by, a CYP-mediated drug interaction.

In vitro evaluation of trifluridine and tipiracil hydrochloride was conducted using human uptake and efflux transporters (trifluridine with MDR1, OATP1B1, OATP1B3 and BCRP; tipiracil hydrochloride with OAT1, OAT3, OCT2, MATE1, MDR1 and BCRP). Neither trifluridine nor tipiracil hydrochloride was an inhibitor of or substrate for human uptake and efflux transporters based on *in vitro* studies, except for OCT2 and MATE1. Tipiracil hydrochloride was an inhibitor of OCT2 and MATE1 *in vitro*.

2.3.4. Toxicology

Single dose toxicity

Table 13: Single dose toxicity studies with TAS-102, FTD and TPI

Study ID	Species/ Sex/Number/ Group	Dose (mg/kg) /Route	Approx. lethal dose mg/kg	Major findings
B-3685 GLP	Rat M+F/5	TAS-102 250, 500, 1000, 2000 Oral gavage	2000	2000: mortality (1M, 4F), bw↓, erosion and necrosis in gastro-intestinal tract
87931 GLP	Dog M+F/1	TAS-102 250, 500, 1000, 2000 Oral gavage	2000 (M) >2000 (F)	≥250: emesis, soft/liquid feces, fc↓, ≥500: bw↓ 2000: mortality (1M), sclerosis lung, necrosis in gastro-intestinal tract
B-3751 GLP	Rat M+F/5	FTD 250, 500, 1000, 2000 Oral gavage	2000	2000: mortality (2M, 3F), bw↓, small thymus and spleen (M), necrosis in gastro-intestinal tract
87930 GLP	Dog M+F/1	FTD 250, 500, 1000, 2000 Oral gavage	>2000	≥250: Emesis, feces↓, bw↓, fc↓ ≥500: necrosis in gastro-intestinal tract
97-19 GLP	Rat M+F/5	TPI 2000 Oral gavage	>2000	2000: salivation, white feces

Fc=food consumption, bw= body weight

Mortality of male and female rats was observed at single oral doses of 2000 mg/kg TAS-102 and FTD. One male dog was sacrificed showing moribund condition at 2000 mg/kg TAS-102. No mortality was observed after a single dose of 2000 mg/kg FTD in dog or 2000 mg/kg TPI in rats.

Repeat dose toxicity

Table 14: Pivotal repeat-dose toxicity studies with TAS-102

Study ID	Species/Sex/ Number/Group	Dose (as mg FTD/kg) /Route	Duration	NOAEL (mg/kg/ day)	Major findings

Study ID	Species/Sex/Number/Group	Dose (as mg FTD/kg) /Route	Duration	NOAEL (mg/kg/day)	Major findings
B-3687 GLP	Rat M/5	0, 15, 50, 150, 450 Oral gavage	2 weeks	50	≥150: Necrosis glandular epithelial in duodenum, jejunum, ileum and rectum↑, follicular atrophy mesenteric / submandibular lymph nodes ↑ 450: Bw gain↓, fc↓, white blood cell and reticulocyte count ↓, necrosis cecal glandular epithelial, thymic atrophy↑
B-3906 GLP	Rat M+F/12	0, 50, 150, 450 Oral gavage	1 month/ 1 month recovery period for 6 animals/ sex/dose	50	≥150: Bw↓ (F), fc↓(F), 450: Bw gain↓, fc↓, red blood cell hemoglobin, hematocrit, white cell, reticulocytes(M), fibrinogen (M) ↓, Corpuscular vol ↑(M), total protein↓, γ-globulin ↓, cholesterol↑ (F), bilirubin↑(F),
07CA07 GLP	Rat M+F/12	0, 5, 15, 50, 150 Oral gavage	3 months/ 2 months recovery period for 6 animals/ sex/dose	15	≥50: White blood cell count↓(F) Disarrangement of odontoblasts and oseodentin↑ in incisors, apoptotic bodies in epithelial cells small intestine↑, fatty infiltration in bone marrow↑ 150: Discoloration, breakage and malocclusion of incisors↑, bw↓ fc↓, white bloodcell count↓, red bloodcell count ↓ (M), mean corpuscular hemoglobin↑, apoptotic bodies in epithelial cells small intestine↑, fatty infiltration in bone marrow↑
87935 GLP	Dog M/3	0, 17, 50, 150 Oral gavage	2 weeks	N.D.	17: Protein and blood in urine and fecal blood↑, thymus weight↓, ≥17: Emesis, fc↓, bw↓ soft/liquid/reduced, black and red feces ↑, Thinnes↑, white blood cell, segmented neutrophil and lymphocyte count↓,dark foci in intestines↑glandular/cryptal necrosis in the gastrointestinal tract, hypocellularity of bone marrow, lymphoid atrophy of the thymus, spleen, lymph nodes and intestines↑ ≥50: Mortality (50: 1M, 150: 1M), activity↓, cold to touch, tremors, weakness, red blood cell count, haemoglobin and haematocrit↑, raised, dark, firm areas and hemorrhagic pneumonia in lungs↑
87936 GLP	Monkey M+F/3	0, 1.9, 7.5, 30, 120 Oral gavage	2 weeks	1.9	≥7.5: white blood cell and lymphocyte count ↓, ≥30: Liquid/soft feces↑ (F), salivation ↑, Typhlitis, colitis, villous atrophy duodenum, jejunum and ileum, lymphoid atrophy spleen germinal center↑ , 120: Mortality (1M, intestinal parasite), liquid/soft feces↑, emesis↑, cryptal necrosis in colon+cecum↑, hematopoietic hypocellularity in bone marrow↑, atrophy mesenteric lymph nodes↑, severity of gastritis ↑ (F)
87941 GLP	Monkey M+F/3	0, 6.25, 25, 100	1 month / 1 month recovery period for 2 animals/ sex/ dose, except 6.25 dose	6.25	≥25: soft/liquid stool↑, emesis↑, dehydration↑, red/white blood cell↓, haemoglobin↓, haematocrit↓, small thymus, raised/dark areas on cecum, inflammatory lesions of cecum (M)/colon (F), lymphoid atrophy spleen, mandibular/mesenteric lymph nodes and gut-associated lymphoid tissue↑ 100: bw↓(M), mean platelet volume↓, corpuscular haemoglobin↑, platelet count↑, Urea nitrogen, creatinine and alanine aminotransferase↑, hematopoietic hypocellularity in bone marrow, gastritis, villous atrophy and cryptal degeneration/regeneration of the small intestine, inflammatory lesions in large intestine, lymphoid atrophy in thymus, myeloid erythroid ratio ↓

Study ID	Species/Sex/ Number/Group	Dose (as mg FTD/kg) /Route	Duration	NOAEL (mg/kg/ day)	Major findings
B-6227 GLP	Monkey M+F/3	0, 1.25, 5, 20 **FTD** 20 Oral gavage	3 months / 2 month recovery period for 2 animals/ sex/dose, except 1.25 TAS-102	TAS-102 1.25 FTD 20	TAS-102: ≥1.25: sporadic emesis ≥5: bw↓, fc↓, red blood cell count↓ 20: Mortality (1F, soft/watery stool↑, lateral position, hypothermia, necrosis and/or atrophy in small intestines), soft/watery stool↑, bw↓, fc↓, white blood cell count, lymphocytes↓(M), haemoglobin↓, haematocrit↓, figrinogen↑, inflammatory cell infiltration rectum↑, atrophy of spleen↑ **FTD:** 20: sporadic emesis

Fc=food consumption, bw= body weight

Table 15: Pivotal and non-pivotal repeat-dose toxicity studies with FTD

Study ID	Species/Sex/ Number/Group	Dose (mg/kg) /Route	Duration	NOAEL (mg/kg/ day)	Major findings
B-3836 GLP	Rat M/5	0, 15, 50, 150, 450 Oral gavage	2 weeks	50	≥150: bw↓ 450: unkempt fur, fc↓, reticulocyte ratio↓, white bloodcell count↓, small thymus, small seminal vesicles, decrased spleen weight, atrophy hemo-lymphatic system, necrosis of glandular epithelial cells. 450: Mortality (3M, soft feces, diarrhea, decreased activity, unkempt fur, emaciation, fecal occult blood, urinary glucose and bilirubin, distension of stomach, focal reddening of small intestine, small thymus, spleen, semical vesicle and prostrate, mucosal atrophy and necrosis of glandular epithelium of intestines, atrophy of hemo-lymphatic system, atrophy of seminiferous tubules, decreased sperm, increased cellular debris in epididymis tubuls, swelling of liver sinusoidal lining cells).
B-3927 GLP	Rat M+F/12	0, 15, 50, 150 Oral gavage	1 month/ 1 month recovery period for 6 animals/ sex/dose, except 15 mg/kg/day	50	≥150: bw↓, fc↓, whitish incisors, white bloodcell count↓, fibrinogen↓, triglycerides↓, potassium blood↑, potassium+chloride in urine↓, crystal in urine (M), ovary weight↑, dark red spot+erosion in stomach, necrosis glandular epithelial cells small intestines, thymus weight↓
87934 GLP	Dog M/3	0, 2, 6, 17 Oral gavage	2 weeks	2	6: mean absolute segmented neutrophils, monocytes eosinophils↓, small thymus, cryptal necrosis intestine, mucosal atrophy stomach, hypocellularity bone marrow, lymphoid atrophy thymus, spleen, lymph nodes and intestines. ≥6: fc↓, white blood cell count↓ , bilirubin in urine, 17: Mortality (3M), bw↓, emesis, soft liquid reduced feces, activity↓, thinnes, dehydration, cold to touch, hunched posture, labored breathing, weakness, tremors, platelet count↓, Serum: albumin globulin ratio, potassium, chloride↓, Serum: bilirubin, alkaline phosphatase, cholesterol, triglycerides, globulin↑, blood, glucose and protein in urine,

Study ID	Species/Sex/Number/Group	Dose (mg/kg) /Route	Duration	NOAEL (mg/kg/day)	Major findings
88308 GLP	Monkey M+F/3	0,1.56, 6.25, 25 Oral gavage	1 month/ 1 month recovery period for 2 animals/ sex/dose, except 1.56 mg/kg/day	25	1.56+25: slight to mild atrophy of intestines
09CB04 Non-GLP Non-pivotal	Monkey M/2	0, 50, 100, 150	1 month	N.D.	≥50: adverse effects in lymphatic and hematopoietic system, gastrointestinal tract, kidney, liver, adrenal gland, testis, epididymis and skin. ≥100: mortality (100: 2M, 150: 2M)

Table 16: Pivotal and non-pivotal repeat-dose toxicity studies with TPI

Study ID	Species/Sex/Number/Group	Dose (mg/kg) /Route	Duration	NOAEL (mg/kg/day)	Major findings
97-20 GLP	Rat M/5	0, 80, 400, 2000 Oral gavage	2 weeks	N.D.	None
98-04 GLP	Rat M+F/12	0, 80, 400, 2000 Oral gavage	1 month/ 2 week recovery period for 6 animals/ sex/dose, except 80 mg/kg/day	2000	Crystalline sediment and white clouding in the urine
88309 GLP	Monkey M+F/3	0, 100, 300, 1000 Oral gavage	1 month/ 1 month recovery period for 2 animals/ sex/dose, except 100 mg/kg/day	100	≥300: soft liquid feces, inflammatory lesions in large intestine and thymic lymphoid atrophy 1000: dark areas of stomach, gastritis, gastric mucosal hemorrhage, mixed cell infiltration in gall bladder, lymphoid hyperplasia of mesenteric lymph node and infiltration of foamy macrophages with lymphoid atrophy of spleen cells

Genotoxicity

TAS-102 and FTD scored positive in all three pivotal genotoxicity assays, with and without metabolic activation and are therefore considered genotoxic. TPI scored negative in all three pivotal genotoxicity assays, with or without metabolic activation and is therefore considered not genotoxic.

Carcinogenicity

In accordance with ICH S9, no carcinogenicity studies have been performed.

Reproduction Toxicity

The effect on fertility and reproduction of TAS-102 were performed in accordance with ICH M3(R2). Fertility in male and female Sprague-Dawley rat was not affected up to a dose of 450 and 150 mg/kg/day TAS-102, respectively. In a 2-week repeated dose study, 450 mg/kg/day FTD alone was observed to induce atrophy of seminiferous tubules, decreased sperm, increased cellular debris in epididymis tubules, swelling of liver sinusoidal lining cells. These effects are expected due to the mechanism of action of FTD. Effects are observed

at systemic concentrations below the human recommended dose.

TAS-102 induced teratogenicity and embryo foetal mortality at 150 mg/kg/day and impaired embryo-foetal growth in absence of maternal toxicity at 50 mg/kg/day. Developmental toxicity is expected due to the mechanism of action of TAS-102 and is observed in animals at a concentration lower than the human intended dose.

No peri- and postnatal toxicology studies have been performed.

Toxicokinetic data

Table 17: Toxicokinetics after exposure to TAS-102:

Study ID	**Daily Dose (mg/kg)**	**Animal $AUC_{(0-24)}$ (ng.h/ml)**		**Animal:Human Exposure Multiple (not corrected for protein binding)**	
		♂	♀	♂	♀
Rat 2 weeks B-3687	50 (day 14)	AUC FTD:6186 FTY:43686 TPI:1405	-	FTD: 0.13 FTY: 4.20 TPI: 1.89	-
Rat 1 month B-3906 Cmax (ng/ml)	50 (day 28)	Cmax (ng/ml) FTD : 6239 FTY : 21331 TPI : 449	Cmax (ng/ml FTD :7636 FTY : 22577 TPI :545	Based on Cmax FTD: **1.28** FTY: **31.4** TPI:**6.47**	Based on Cmax FTD: **1.57** FTY: **33.3** TPI: **7.86**
Rat 3 months 07CA07	15 (week 13)	FTD : 1800 FTY : 13500 TPI : 424	FTD : 2550 FTY : 15000 TPI : 492	FTD :0.04 FTY :1.30 TPI :0.57	FTD :0.05 FTY :1.44 TPI :0.66
Dog 2 weeks 87935	17 (week 2)	FTD :11528 FTY : 58783 TPI : 3253	-	FTD :0.24 FTY :5.65 TPI :4.37	-
Monkey 2 weeks 87936	1.9 (week2)	FTD :1149 FTY : 997 TPI : 42	FTD :1309 FTY : 1528 TPI : 31	FTD :0.02 FTY :0.10 TPI :0.06	FTD :0.02 FTY :0.15 TPI :0.04
Monkey 1 month 87941	6.25 (day 28)	No AUC data available			
Monkey 3 months B-6227	TAS-102 1.25 (week 13) FTD 20 (week 13)	TAS-102 FTD :3200 FTY :1550 TPI :257 FTD FTD :675 FTY :35100 TPI : ND	TAS-102 FTD :1670 FTY :1420 TPI :140 FTD FTD :433 FTY :35800 TPI : ND	FTD :0.07 FTY :0.15 TPI :0.35	FTD :0.04 FTY :0.14 TPI :0.19
Human 12 days TPU-TAS-102-102	TAS-102 70 mg/day (day 12)	FTD* : 47392 FTY* : 10412 TPI* : 744		-	-

ND=not detected; AUC_{0-24h} calculated from AUC_{0-12}

Table 18: Toxicokinetics after exposure to FTD:

Study ID	**Daily Dose (mg/kg)**	**Animal $AUC_{(0-24)}$ (ng.h/ml)**		**Animal:Human Exposure Multiple (not corrected for protein binding)**	
		♂	♀	♂	♀

Study ID	Daily Dose (mg/kg)	Animal $AUC_{(0-24)}$ (ng.h/ml)		Animal:Human Exposure Multiple (not corrected for protein binding)	
		♂	♀	♂	♀
Rat 2 weeks B-3836	50 (day 14)	FTD : 2357 FTY : 38007	-	FTD :0.05 FTY :3.65	-
Rat 1 month B-3927	50 (day 28) :	No AUC data available			
Dog 2 weeks 87934	2 (day 14)	FTD :187 FTY :2712	-	FTD :0.004 FTY :0.26	-
Monkey 1 month 88308	25 (day 22)	FTD : 236 FTY : 37158	FTD : 290 FTY : 33388	FTD :0.005 FTY :3.57	FTD :0.006 FTY :3.20

ND=not detected

Table 19: Toxicokinetics after exposure to TPI:

Study ID	Daily Dose (mg/kg)	Animal $AUC_{(0-24)}$ (ng.h/ml)		Animal:Human Exposure Multiple (not corrected for protein binding)	
		♂	♀	♂	♀
Rat 1 month 98-04	2000 (day 27)	TPI :23092	TPI :27004	TPI :31.0	TPI :36.3
Monkey 1 month 88309	100 (day 22)	TPI :10918	TPI :8440	TPI : 14.6	TPI : 11.3

ND=not detected

Local Tolerance

No stand-alone local tolerance studies were conducted.

Other toxicity studies

Phototoxicity

The phototoxic potential of FTD and TPI were tested in Balb/3T3 clone A31 cells using Neutral Red uptake. No photo-toxicity was observed for either compound.

Combination toxicology of TAS-102 with Azidothymidine

A combination study with TAS-102 (450 mg/kg/day) and azidothymidine (AZT) (167 mg/kg/day) was performed in male rats. AZT did not induce any adverse effects and did not enhance adverse effects induced by TAS-102.

2.3.5. Ecotoxicity/environmental risk assessment

Trifluridine

Parameter	Study ID/GLP	Protocol	Results	Criterion	Conclusion
Bioaccumulation	Reference /	Shake flask,	Log D_{ow} = -0.425	log K_{ow} > 4.5	Not B

	unknown	pH 2-12 were tested	at pH 6		

Trifluridine is considered not to be a PBT or vPvB substance.

The refined PECsw is 0.002 µg/L for trifluridine, which is below the action limit of 0.01 µg/L. Therefore , a phase II assessment is not warranted.

Tipiracil

Parameter	Study ID/GLP	Protocol	Results	Criterion	Conclusion
Bioaccumulation	Not provided	Shake flask, pH 2-12 were tested	Log D_{ow} = -4.25 at pH 2; -3.16 at pH 4; -2.30 at pH 6; -2.03 at pH 7; -1.97 at pH 8; -1.95 at pH 10; -2.01 at pH 12	log K_{ow} > 4.5	pm

Tipiracil is considered not to be a PBT or vPvB substance.

The refined PECsw is 0.0009 µg/L for tipiracil, which is below the action limit of 0.01 µg/L. Therefore, a Phase II assessment is not warranted.

2.3.6. Discussion on non-clinical aspects

Lonsurf or TAS-102 is a combination of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic thymidine-based nucleoside analogue, which is incorporated into deoxyribonucleic acid (DNA) in tumour cells following phosphorylation and metabolism.

TPI inhibits degradation of FTD by inhibiting thymidine phosphorylase (TPase), thus increasing systemic exposure to FTD when FTD and TPI are given together. This pharmacodynamic action follows from data submitted in the pharmokinetic part of the dossier.

In vitro evaluation indicated that trifluridine and FTY had no inductive effect on human CYP1A2, CYP2B6 or CYP3A4/5. Thus trifluridine is not expected to cause or be subject to a significant medicinal product interaction mediated by CYP. In the *in vitro* induction study evaluating the inductive effect of tipiracil on human CYP isoforms, the concentration of tipiracil in the study was too low to investigate the potential induction in intestinal cells. Inductive effect of tipiracil on human CYP isoforms cannot be excluded (see section 5.2 of the SmPC). The applicant is recommended to further investigate the potential induction of intestinal CYP3A4 by tipiracil at relevant concentrations.

Tipiracil hydrochloride was an inhibitor of OCT2 and MATE1 *in vitro*, but at concentrations substantially higher than human plasma C_{max} at steady state. Thus it is unlikely to cause an interaction with other medicinal products, at recommended doses, due to inhibition of OCT2 and MATE1. Transport of tipiracil hydrochloride by OCT2 and MATE1 might be affected when Lonsurf is administered concomitantly with inhibitors of OCT2 and MATE1.

Humans exposed to single dose of FTD have AUC of 7120-10082 ng.h/ml and when exposed to a single dose of TPI have an AUC of 302-392 ng.h/ml. Doses tested in Safety pharmacology studies resulted in more than 5 times higher exposure than human exposure, thus dose levels are regarded to be sufficiently high.

It can be anticipated from the conducted secondary pharmacology screen that no secondary pharmacological effects will occur in human upon dosing with Lonsurf according to the clinical dosing regimen.

Toxicology assessment of trifluridine/tipiracil hydrochloride was performed in rats, dogs and monkeys. The target organs identified were the lymphatic and haematopoietic systems and the gastrointestinal tract. All changes, i.e., leucopenia, anaemia, bone marrow hypoplasia, atrophic changes in the lymphatic and haematopoietic tissues and the gastrointestinal tract, were reversible within 9 weeks of drug withdrawal. The fact that a large relative portion of the drug is taken up into DNA may contribute to the MoA, which may also explain observed toxicity effects in GI tract and the hematopoietic system consisting of rapidly dividing cells. Whitening, breakage, and malocclusion were observed in teeth of rats treated with trifluridine/tipiracil hydrochloride, which are considered rodent specific and not relevant for human (see section 5.3 of the SmPC).

Corrected for protein binding, exposure to FTD when given TAS-102 in rat and monkeys at the NOAEL was, respectively, 0.03-0.16 times and 0.06-0.2 times the exposure in humans at the intended dose.

Dogs appear to be very sensitive to TAS-102 and FTD. Target organs affected by TAS-102 in dogs are similar compared to those affected in rat and monkey, however, adverse effects in dogs seem to be more severe compared to rat and monkey. Corrected for protein binding, exposure to FTD by TAS-102 in dog at 17 mg/kg/day is ca. 4x higher than in human at the recommended dose. However, 17 mg/kg/day is not the NOAEL. In the repeated dose study with FTD in dogs, the NOAEL was established at 2 mg/kg/day, which corresponded to a safety factor of 0.004. Corrected for protein binding, the safety factor is 0.07. Although the Applicant does not discuss the increased sensitivity of dogs to TAS-102, the dog can be regarded as a too sensitive model in view of scientific relevance and animal welfare.

In rat, the type of adverse effects observed after FTD exposure alone were similar, but more severe compared to TAS-102. Furthermore, FTD levels were 2x lower in FTD exposure alone compared to TAS-102 exposure. Also in dog, at comparable levels of FTD, adverse effects observed after FTD exposure alone were more severe than after exposure to TAS-102. The cause of more severe effects observed in rat and dog at a similar or lower AUC after FTD exposure compared to TAS-102 is not clear, but may be related to relatively high scatter in AUC-data.

After one week exposure, at a dose of 25 mg/kg/day FTD in TAS-102, adverse toxicological effects were observed in the monkey, whereas no effects were observed after treatment with FTD alone. This is due to the decreasing metabolization of FTD by TPI in TAS-102 as the concentration ratio FTD:FTY is 1:50 in FTD exposure alone (based on Cmax) and 4:1 in TAS-102 (based on concentration 2 hours after exposure). Due to absence of any effect in the one month monkey study, FTD was tested in one monkey at 100 and 150 mg/kg/day, which proved to be lethal. In our opinion, it was not necessary to perform a subsequent study in monkey, as severe toxicity was already established in the study with one monkey. The added value of the additional study in light of scientific relevance and animal welfare is therefore highly questioned.

In rat and monkey models, at similar doses of FTD, less FTY metabolite was formed after exposure to TAS-102 compared to FTD alone, whereas in dog, no difference in FTY formation was observed between exposure to FTD alone and TAS-102. This indicates the intended mechanism of action of TPI is observed in rat and monkey, but not in dog.

Animal: human exposure multiples corrected for protein binding were less than 1 for FTD after exposure to TAS-102 and FTD, whereas the major metabolite FTY was below 1 only in monkey after exposure to TAS-102. TPI was found not to induce adverse effects at exposure multiples of at least 11x. As adverse effects induced by FTD are part of its mechanism of action, the low exposure multiples after treatment with TAS-102 in monkeys may be of relevance for the human situation.

No long term studies evaluating the carcinogenic potential of trifluridine/tipiracil hydrochloride in animals have been performed. Trifluridine was shown to be genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammal-cultured cells, and a micronucleus test in mice. Therefore, Lonsurf should be treated as a potential carcinogen (see section 5.3 of the SmPC).

Results of animal studies did not indicate an effect of trifluridine and tipiracil hydrochloride on male and female fertility in rats. The increases in the corpus luteum count and implanting embryo count observed in female rats at high doses were not considered adverse). Lonsurf has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. No peri/post-natal developmental toxicity studies have been performed.

Trifluridine may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking Lonsurf and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf and for 6 months after stopping treatment. It is currently unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method. Male patients should be using effective contraception during treatment and for up to 6 months after discontinuation of treatment.

It is unknown whether Lonsurf or its metabolites are excreted in human milk. Studies in animals have shown excretion of trifluridine, tipiracil hydrochloride and/or their metabolites in milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Lonsurf (see sections 4.6 and 5.3 of the SmPC).

The absence of local tolerance studies was considered acceptable as the clinical route of administration of TAS-102 is oral, and histopathological evaluation of the tongue, oesophagus and gastro-intestinal tract were assessed as part of the repeated dose toxicity studies.

Trifluridine and Tipiracil are both considered not to be a PBT or vPvB substance.

The refined PECsw is 0.002 and 0.0009 µg/L for trifluridine and tipiracil, respectively. This is below the action limit of 0.01 µg/L. Therefore, a Phase II assessment is not warranted for trifluridine and tipiracil .

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted are considered sufficient to support the evaluation of the benefit risk of Lonsurf.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 20: Overview of clinical phase I studies conducted in the US

Study No.	Study Design	Dosage and Administration	Main Items Examined
TAS102-9801	Open label nonrandomized dose determining study	Administration: 14 day once daily (qd) administration followed by seven drug-free days /1 cycle Dosage: 50-, 60-, 100- mg/m^2/day	MTD, RD, safety profile, antitumor effect, pharmacokinetics
TAS102-9802	Open label nonrandomized dose determining study	Administration: 2 sessions of treatment (5 day once daily, qd x 5, administration followed by two drug-free days) followed by 14 drug-free days /1 cycle Dosage: 50-, 70-, 80-, 90-, 100-, 110- mg/m^2/day	
TAS102-9803	Open label nonrandomized dose determining study	Administration: 5 day once daily (qd) administration followed by 16 drug-free days /1 cycle Dosage: 100-, 110-, 120-, 130-, 140-, 150-, 160-, 170-, 180- mg/m^2/day	
TAS102-9804	Open label nonrandomized dose determining study	Administration: 2 sessions of treatment (5 day twice daily, BID x 5, administration followed by two drug-free days) followed by two drug-free weeks /1 cycle Dosage: 50-, 60-, 80- mg/m^2/day	
TAS102-9805	Open label nonrandomized dose determining study	Administration: 2 sessions of treatment (5 day three times daily, TID x 5 administration followed by two drug-free days) followed by two drug-free weeks /1 cycle Dosage: 60-, 70-, 80- mg/m^2/day	

Table 21: Description of Clinical Efficacy and Safety Studies

Type of Study	Study Identifier Sites Country	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Patients	Diagnosis of Patients	Duration of Treatment	Median Age, yrs (Range) Sex (%), M/F Race (%), W/A/O	Study Status Type of Report
Controlled efficacy and safety studies/ claimed indication	TPU-TAS-102-301 RECOURSE 101 study sites USA: 21 Japan: 20 Spain: 11 Italy: 9 Germany: 8 Belgium: 6 France: 6 Australia: 5 UK: 5 Austria: 4 Ireland: 3 Sweden: 2 Czech Republic: 1	Compare TAS-102 + BSC with placebo + BSC for the following endpoints: Primary OS Key secondary PFS, safety and tolerability Other secondary TTF, ORR, DCR, and DR subgroup analysis by *KRAS* status (OS and PFS) Exploratory Effect of intrinsic and extrinsic factors on PK of TAS-102 Concentration-response analyses	Phase 3, placebo-controlled, multicenter, double-blind, parallel, randomised PK assessments at selected sites	TAS-102 tablets, 15 and 20 mg matching placebo tablets, 15 and 20 mg TAS-102 or placebo 35 mg/m^2 PO BID for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks	N=800 (ITT population) TAS-102: 534 Placebo: 266	Patients with mCRC who had received ≥2 prior regimens of standard chemotherapies (including fluoropyrimidine, irinotecan, and oxaliplatin, an anti-VEGF monoclonal anti-body; and at least 1 anti-EGFR monoclonal anti-bodies for *KRAS* wild-type patients) and were refractory to or failing those chemotherapies	28 days/cycle, continued until discontinuation criterion met	TAS-102: 63 (27-82) 61/39 57/35/8 Placebo: 63 (27-82) 62/38 58/35/6	Ongoing Data cutoff: 24Jan2014 (survival data); 31Jan2014 (non-survival data) Final report 26Aug2014 Revised 20Nov2014 39 patients remained on study treatment at data cutoff Ann Oncol 2014;25 (Suppl 2; abstr O-0022) Ann Oncol 2014;25 (Suppl 5; abstr LBA13)

Controlled efficacy and safety studies/ claimed indication	J003-10040030 20 study sites Japan	Primary Compare TAS-102 and placebo groups with respect to OS Secondary Compare TAS-102 and placebo groups with respect to RR, DR, DCR, PFS, TTF, AE profile and tolerability, and effect of TAS-102 with respect to *KRAS* mutation Exploratory FTD DNA damaging action Correlation between protein expression and clinical effect	Phase 2, placebo-controlled, multicenter, double-blind, randomised,	TAS-102 tablets, 15 and 20 mg matching placebo tablets, 15 and 20 mg TAS-102 or placebo 35 mg/m^2 PO BID for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks	N=170 (all treated patients) TAS-102: n=113 Placebo: n=57 N=169 (FAS population) TAS-102: n=112 Placebo: n=57	Patients with unresectable advanced/ recurrent CRC who had received ≥2 chemotherapy regimens and who were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin	28 days/cycle, continued until discontinuation criterion met	TAS-102: 63 (28-80) 57/43 0/100/0 Placebo: 62 (39-79) 49/51 0/100/0	Complete Data cutoff: 13Apr2011 Final report 31Aug2011 Lancet Oncol 2012;13: 993-1001
A=Asian; AE = adverse events; BID = twice daily; BSC = best supportive care; CRC = colorectal cancer; DCR = disease control rate; DNA = deoxyribonucleic acid; DR = duration of response; EGFR = epidermal growth factor receptor; F=female; FAS=full analysis set; FTD=trifluridine; ITT = intent to treat; *KRAS* = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; M=male; mCRC = metastatic colorectal cancer; O=Other; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PK = pharmacokinetic(s); PO = by mouth; RR = response rate; TTF = time to treatment failure; UK = United Kingdom; USA = United States of America; VEGF = vascular endothelial growth factor; W=white/Caucasian									

Table 22: Overview of clinical pharmacology studies

Phase	Clinical PK and Tolerability Studies		
	Japan	Western Patients (US/UK)	Global
Phase 1	J001-10040010 (Dose-finding) J004-10040040 (Food Effect)	TPU-TAS-102-101 (Dose-finding) TPU-TAS-102-102 (TPI Contribution) TPU-TAS-102-103 (QTc Study) TPU-TAS-102-104 (Bioavailability)	
Phase 3			TPU-TAS-102-301 (RECOURSE) (Population PK)

PK=pharmacokinetic; US=United States; UK=United Kingdom of Great Britain and Northern Ireland.

2.4.2. Pharmacokinetics

The clinical pharmacology program has been conducted for TAS-102 in patients with advanced solid tumours, and in patients with metastatic CRC. Given the anti-neoplastic character of trifluridine, no studies have been conducted in healthy volunteers.

The clinical pharmacology program consisted of basic pharmacokinetic (single- and multiple-dose, absorption, distribution, metabolism, and excretion, drug-drug interaction, food effect and relative bioavailability, and pharmacokinetics in Japanese and Caucasian patients) properties of trifluridine and tipiracil in patients with advanced solid tumours or metastatic CRC, population PK analysis, exposure-effect relationships in patients, exposure QTc relationships in patients. Additionally, in vitro studies with human biomaterials were performed in order to assess the potential of trifluridine and tipiracil to act either as a substrate, inhibitor, or inducer of drug metabolizing enzymes and drug transporters.

Ongoing or planned studies include studies to evaluate the PK of Lonsurf components/metabolites in patients with renal impairment (TO-TAS-102-107) and hepatic impairment (TO-TAS-102-106), a Phase I dose-escalating, safety, tolerability, and pharmacokinetic study of TAS-102 with CPT-11 in patients with advanced gastrointestinal tumours (TPU-TAS-102-109), a Phase I, open-label, non-randomised, pharmacokinetic study of TAS-102 in Chinese patients with solid tumours (10040100), a randomized,

double-blind, Phase III Study of TAS-102 versus placebo in Asian (China, South Korea and Thailand) patients with metastatic CRC refractory or intolerable to standard chemotherapies (10040090), and an open-label expanded access Phase IIIb study of TAS-102 in patients with metastatic colorectal cancer refractory to or failing standard chemotherapy (TO-TAS-102-401). A study to assess the mass balance of orally administered trifluridine and tipiracil as components of TAS-102 (TPU-TAS-102-108) was submitted during the procedure.

Methods

The plasma and urine concentrations of the parent compound trifluridine, its major metabolite 5 trifluoromethyluracil (FTY), and tipiracil were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS) after administration of TAS-102. Analytical methods for trifluridine (and its metabolites) and tipiracil were adequately validated.

PopPK analysis

The structural model for trifluridine was a 1-compartment disposition model with transit absorption model (nt=4). A covariance structure for the 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 (nt=4). A covariance structure for the IIV between Vd/F and CL/F was included in the base and final model.

In the popPK model no single dose data have been included in the model. Single dose data were not included because the 3-fold increase in trifluridine could not be modelled according to the applicant and the multiple dose data were considered more relevant for correlation with efficacy and safety. Sufficient PK rich data set was available following multiple dosing to develop a popPK model.

Goodness-of-fit plots for population was not impressive but the popPK model predicted the individual plasma concentration reasonably well; there is underestimation of the higher concentrations of trifluridine and tipiracil and some overestimation of the lower concentrations. VCP plots and individual overlay plots confirmed that plasma samples were sufficiently well predicted although the exposure in subjects with slow absorption was less well predicted. Vd/F, CL/F, MTT parameters seem to be estimated with acceptable precision because their relative standard errors (%) and shrinkages (%), and residual errors were below 30%.

Absorption

Following Lonsurf administration, trifluridine and tipiracil are rapidly absorbed with mean Tmax values of 1-2 hours for trifluridine and 2-3.5 hours for tipiracil. At day 12 of cycle 1, treatment with TAS-102 35 mg/m^2 resulted in mean trifluridine AUC values ranging from 20950 and 24546 ng*h/ml, Cmax from 4752 and 5548 ng/ml for studies in Japanese as well as Caucasian patients (J001-10040010, TAS-102-102, and TAS-102-103). Mean tipiracil AUC values varied between 317-382 ng*h/ml and mean Cmax between 69 and 79 ng/ml.

No absolute bioavailability study has been conducted with TAS-102 to evaluate the oral bioavailability of trifluridine and tipiracil. Absorption of trifluridine is estimated >57% to almost complete and >27% but <50% for tipiracil based on urinary and fecal excretion of trifluridine related compounds and tipiracil related compounds in the mass balance study TAS-102-108.

Trifluridine and tipiracil are high soluble, i.e., 60 mg/ml and 120 mg/ml, respectively, in aqueous solutions over pH range pH 1.2-7.5. Based on the estimated absorption from the mass balance study and the high solubility, trifluridine and tipiracil are classified as BCS class 3 substances.

Permeability of trifluridine in Caco-2 was concentration dependent, more pronounced in the B-A direction and was affected by inhibitors verapamil and 2,4-dinitrophenol. These results indicate the involvement of transporter in bidirectional fluxes of trifluridine across Caco-2 cell monolayers.

Bioavailability

Trifluridine is rapidly degraded by intestinal and liver thymidine phosphorylase (thymidine phosphorylase). Tipiracil is an inhibitor of thymidine phosphorylase. Study TAS-102-102evaluated the effect of tipiracil on the bioavailability of trifluridine at a TAS-102 dose of 35 mg/m^2. Trifluridine AUC was 37-fold higher following administration of TAS-102 than following administration of trifluridine alone. The trifluridine C_{max} was 22-fold higher for TAS-102 compared to trifluridine alone. These findings support the contribution of tipiracil, in the combination of trifluridine and tipiracil (Lonsurf).

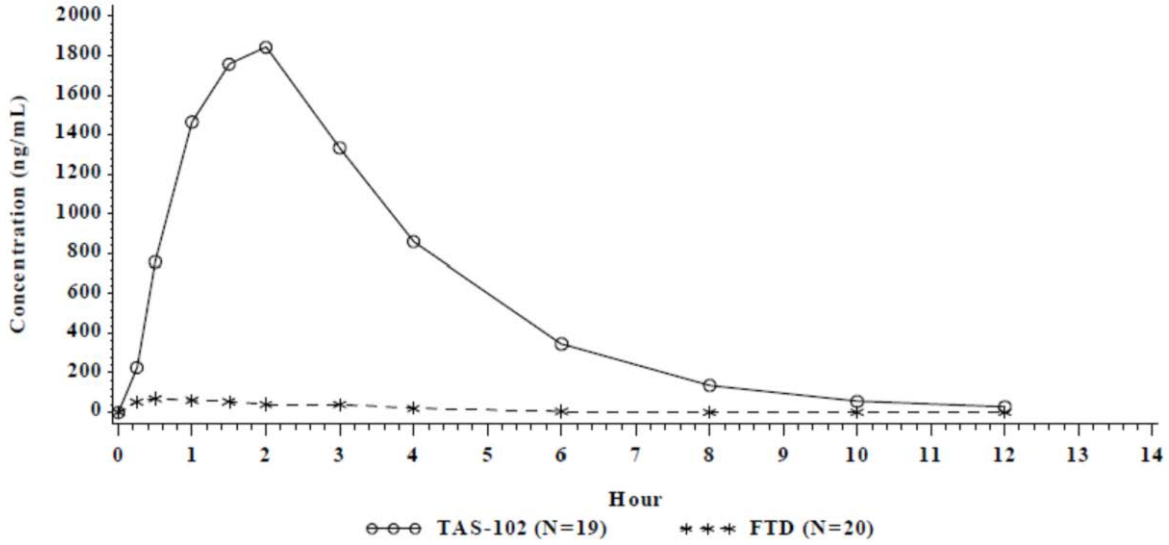


Figure 7. Mean trifluridine Plasma Concentrations Time Profile after Single Dose of TAS-102 or trifluridine Alone (Study TAS-102-102)

Study TAS-102-104 evaluated the relative bioavailability of TAS-102 tablets compared to an oral solution in patients with advanced solid tumours. Bioavailability of trifluridine and tipiracil was comparable following TAS-102 60 mg administration as tablets or solution.

Food

The effect of a high-fat, high-calorie meal on the pharmacokinetics of trifluridine and tipiracil was studied in Study J004-10040040. Trifluridine area under the concentration-time curve (AUC) did not change, but trifluridine C_{max}, tipiracil hydrochloride C_{max} and AUC decreased by approximately 40% compared to those in a fasting state.

Table 23: Food effect on the pharmacokinetics of trifluridine and tipiracil in Japanese patients with solid tumours (study J004-10040040)

Study	J004-10040040	
Dose, Fast/Fed	35 mg/m^2, Fed	35 mg/m^2, Fasted
Number of Patients	N=14	N=14
FTD		
C_{max} (ng/mL)	3510±1380 (39.2)	5630±1840 (32.7)
T_{max} (hr)[b]	1.32 (0.50, 4.00)	0.88 (0.25, 2.00)
AUC_{0-10} (ng*hr/mL)[c]	9840±4247 (43.2)	10648±5011 (47.1)
AUC_{0-inf} (ng*hr/mL)	10082±4593 (45.6)	10943±5581 (51.0)
$T_{½}$ (hr)	1.72±0.58 (33.5)	2.13±0.76 (35.6)
TPI		
C_{max} (ng/mL)	76.8±26.3 (34.3)	135±39 (29.0)
T_{max} (hr) [b]	2.79 (1.00, 6.00)	2.07 (1.00, 4.00)
AUC_{0-10} (ng*hr/mL) [c]	361±160 (44.4)	647±281 (43.4)
AUC_{0-inf} (ng*hr/mL)	384±189 (49.2)	677±309 (45.7)
$T_{½}$ (hr)	2.22±0.45	2.19±0.66
FTY		
C_{max} (ng/mL)	728±186 (25.6)	860±207 (24.1)
T_{max} (hr) [b]	1.96 (0.50, 4.00)	1.43 (1.00, 2.00)
AUC_{0-10} (ng*hr/mL) [c]	3011±855 (28.4)	2900±837 (28.9)
AUC_{0-inf} (ng*hr/mL)	3121±941 (30.2)	2972±868 (29.2)
$T_{½}$ (hr)	2.08±0.69	2.41±0.61

Distribution

The blood/plasma concentration ratios for trifluridine and tipiracil were 0.6 over the concentration range of 0.5-50 µg/mL for trifluridine and 0.010- 1 µg/mL of tipiracil (Study 11DA34), indicating that in human blood, trifluridine and tipiracil are distributed mainly in the plasma fraction.

The plasma protein binding of trifluridine and tipiracil in human serum was determined by ultrafiltration methods (studies AE-2350-2G and AE-2350-3G). The plasma protein binding for trifluridine was high (96%) and independent of the concentration 0.5-50 µg/mL; trifluridine was primarily bound to HSA. The extent of trifluridine binding to plasma protein was not affected by the presence of other albumin-bound drugs (Study No. 12DA05) or tipiracil. Trifluridine did not displace the albumin-bound drug warfarin in human plasma (Study No. 12DA05). Plasma protein binding for tipiracil was low (<8%) over the concentration range 0.05- 5 µg/mL. Tipiracil is a substrate for OCT2 and MATE1 transporters (studies 09DB12 and 12DB11, data not shown). These transporters can be involved in the elimination of tipiracil in urine.

A potential drug interaction caused by plasma protein displacement is low. In the mass balance study using a ^{14}C-trifluridine, > 90% of radioactive material could be recovered from plasma at 2 hours after dosing, but the recovery declined to < 1% at 96 hours and later time points indicating covalent binding of trifluridine related substance with proteins.

Trifluridine is a substrate for nucleoside transporters CNT1, ENT1 and ENT2 (Takahashi K, 2015; Sakamoto K, 2015) which may be involved in the absorption and distribution of trifluridine.

Volume of distribution and oral clearance of trifluridine and tipiracil across studies are summarised in the table below.

Table 24: Oral clearance and apparent volume of distribution of trifluridine and tipiracil in PK studies

	Trifluridine		tipiracil	
	CL/F (L/hr)	**Vd/F(L)**	**CL/F (L/hr)**	**Vd/F(L)**
J001-10040010*				
Day 1	8.73 (1.33)	17.32 (4.00)	135.42 (78.44)	327.08 (198.32)
Day 12	3.53 (0.22)	10.06 (2.81)	139.86 (69.56)	529.84 (498.02)
J001-10040040*				
Fasting	7.84 (4.14)	22.94 (13.39)	57.35 (23.68)	179.08 (92.5)
Fed	8.51(4.44)	19.24(7.55)	99.16 (33.30)	303.4 (91.76)
TPU-TAS-102-102				
TAS-102	10.53 ± 4.46	20.92 ± 9.68	109.33 ± 46.38	332.95 ± 175.70
FTD ALONE	282.90 ± 193.31	486.14 ± 402.88		
TPU-TAS-102-103	9.31 ± 4.23	19.60 ± 10.22	96.19 ± 49.04	273.67 ± 155.40
TPU-TAS-102-104	10.23 ± 5.27	24.23 ±9.41	61.47 ±36.34	182.67 ± 98.32

*For 74 kg

Elimination

Following a single dose of Lonsurf (35 mg/m^2) in patients with advanced solid tumours, the oral clearance (CL/F) for trifluridine and tipiracil hydrochloride were 10.5 L/hr and 109 L/hr, respectively.

The estimated apparent systemic trifluridine CL/F was 2.9 L/h at day 12 of a treatment cycle (popPK analysis).

The estimated tipiracil CL/F following multiple dosing was 88.7 L/h for a typical cancer patient (popPK analysis).

Following the multiple-dose administration of Lonsurf at the recommended dose and regimen, the mean elimination half-life ($t_{1/2}$) for trifluridine on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 1.4 hours and 2.1 hours, respectively. The mean $t_{1/2}$ values for tipiracil hydrochloride on Day 1 of Cycle 1 and on Day 12 of Cycle 1 were 2.1 hours and 2.4 hours, respectively.

Metabolism

In vitro studies showed that trifluridine and tipiracil are not metabolized by CYP enzymes. It was demonstrated that trifluridine is primarily metabolized by thymidine phosphorylase.

In the mass balance study, trifluridine and FTY were the major circulating moieties with 53% and 33%, respectively, of extractable radioactivity. No other peaks greater than 5% of radioactive material were detected. In urine, 53% - 57% of the administered dose was excreted as trifluridine related compounds: ~1% as unchanged trifluridine, ~25% as FTY, ~18% as 2 trifluridine-glucuronide isomers. Other minor metabolites, 5 carboxyuracil and 5-carboxy-2'-deoxyuridine, were detected, but those levels in plasma and urine were at low or trace levels.

TPI is a specific inhibitor of TPase and consequently an inhibitor of the metabolism of trifluridine in the intestinal tract and liver. Due to the low absorption of tipiracil, its activity might be focus in the intestinal tract. In the mass balance study, 6-HMU was the only major metabolite of tipiracil in plasma, urine and faeces: plasma radioactivity consisted of 30.9% 6-HMU and 53.1% tipiracil, radioactivity in urine consisted of 14.0% 6-HMU and 79.1% tipiracil, and the faecal radioactivity consisted of 34.4% 6-HMU and 48.2% tipiracil. 6-HMU appeared in plasma or in blood after disappearance of tipiracil, which indicates that 6-HMU was slowly produced. No other metabolites greater than 5% were observed in plasma, urine and faeces.

Polymorphism

Trifluridine is a substrate for thymidine phosphorylase and thymidine kinase and for human nucleoside transporters. Polymorphism of these enzymes and transporters has not been investigated.

Inter-conversion

Trifluridine and tipiracil are polymorphic; however, given the high solubility of these compounds there is no

difference in the dissolution rate between the polymorphic forms.

Pharmacokinetic of metabolites

The main metabolite of trifluridine is FTY, which in detected in plasma and urine in a relevant concentration. Pharmacokinetic parameters of FTY are summarized in Table 25. The trifluridine-glucuronide isomers were not detected in plasma only in urine.

Table 25: Single-dose TAS-102 PK studies – Mean ± SD (%CV)

Study	J001-10040010	J004-10040040		TPU-TAS-102-102	TPU-TAS-102-103	TPU-TAS-102-104
Dose, Fast/Fed	35 mg/m^2, Fed	35 mg/m^2, Fed	35 mg/m^2, Fasted	35 mg/m^2, Fed	35 mg/m^2, Fed	60-mg fixed dose, Fasted[a]
Number of Patients	N=6	N=14	N=14	N=19	N=44	N=21
FTY						
C_{max} (ng/mL)	878±228 (26)	728±186 (25.6)	860±207 (24.1)	764.89±201.44 (26.34)	904.05±286.95 (31.74)	1093.38±339.55 (31.05)
T_{max} (hr) [b]	2.0 (2.0, 2.0)	1.96 (0.50, 4.00)	1.43 (1.00, 2.00)	2.69 (1.00, 6.08) (46.30)	2.68 (0.58, 6.25) (54.42)	1.57 (0.47, 5.95) (73.06)
$AUC_{0\text{-}10}$ (ng*hr/mL) [c]	3165±341 (11)	3011±855 (28.4)	2900±837 (28.9)	3343.75±897.48 (26.84)	3735.91±1067.64 (28.58)	3643.60±1109.78 (30.46)
$AUC_{0\text{-}inf}$ (ng*hr/mL)	3492±693 (20)	3121±941 (30.2)	2972±868 (29.2)	3435.59±924.88) (26.92)	3809.38±1112.64 (29.21)	3716.41±1120.40 (30.15)
$T_{½}$ (hr)	1.57±0.38 (24)	2.08±0.69	2.41±0.61	1.76±0.38 (21.49)	1.62±0.24 (14.81)	1.66±0.46 (27.54)

Concentrations of tipiracil metabolite, 6-HMU, were low in plasma and Cmax was reached 48h after administration of TAS-102. Approximately 17% of the tipiracil dose was excreted 6-HMU in the feces. tipiracil

Excretion

Urinary excretion of trifluridine, FTY, tipiracil and trifluridine metabolites was evaluated after single dose TAS-102 in relative bioavailability study-TAS-102-104 in the US and in the dose finding study J001-10040010 in Japanese patients.

Of the administered dose, 21% - 25% was excreted as trifluridine related compounds but only a small fraction of the administered dose of TAS-102 was excreted as unchanged trifluridine (1.5 and 3.7%).

Twenty seven (27) % - 29% of the administered dose of tipiracil was excreted in its unchanged form. Renal clearance of tipiracil was 293 ml/min, exceeding the glomular filtration rate suggesting a transporter mediated excretion of tipiracil in the urine, presumably OCT2.

In the mass balance study TAS-102-108, an oral solution incorporating a light tracer dose of either [^{14}C]-trifluridine or [^{14}C]-tipiracil and 60 mg TAS-102 was administered on Day 1 in 8 patients (4 patients received [^{14}C]-trifluridine / 60 mg TAS-102 and 4 patients received [^{14}C]-tipiracil /60 mg TAS-102). Of the administered [^{14}C]-trifluridine, on average, 60% of the radioactivity was recovered, consisting of 54.8% urinary excretion, 2.6% fecal excretion, and 2.4% expired CO2 (see Table 26).The overall recovery of radioactivity was relatively poor probably due to covalent binding to proteins and incorporation in DNA.

Table 26: Excreta PK Parameters and Summary Statistics for Total Radioactivity of [14C]-trifluridine Excreted in Urine, Feces, Respired 14CO2 and Total Recovered – study TAS-102-108

	Urine		Feces	Expired CO_2		TRA
	$Ae\%_R$ (%)	CLr (mL/hr)	$Ae\%_F$ (%)	$AURC_{0\text{-last}}$ (mg-equivalents)	$Ae\%_{CO2}$ (%)	$Ae\%_{total}$ (%)
N	4	4	4	4	4	4
Mean ± SD	54.772 ± 1.7328	414.717 ± 134.8227	2.649 ± 0.3810	1.424 ± 0.5254	2.373 ± 0.8757	59.794 ± 1.5814
%CV	3.2	32.5	14.4	36.9	36.9	2.6
Median	54.179	427.820	2.736	1.250	2.083	59.343
Min – Max	53.42 - 57.31	255.76 - 547.47	2.12 - 3.01	1.00 - 2.19	1.67 - 3.65	58.50 - 61.99

Results of the mass balance study in the subjects administered a tracer dose of or [14C]-tipiracil and 60 mg TAS-102 is shown in the below table. Fecal excretion represented 50 ± 22% of total excretion of the administered dose, while renal excretion accounted for 27 ± 8%. In 1 patient, the overall recovery was extremely poor at 36.3% of the dose (18.8% urine and 17.5% feces), probably due to poor fecal production. For the other 3 patients, the overall recoveries were > 85% and similar across the remaining patients.

Table 27: Excreta PK Parameters and Summary Statistics for Total Radioactivity of [14C]-tipiracil Excreted in Urine, Feces, and Total Recovered – study TAS-102-108

	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

Dose proportionality and time dependencies

Dose proportionality

In a dose finding study (15 to 35 mg/m^2 twice daily), the AUC from time 0 to 10 hours (AUC_{0-10}) of trifluridine tended to increase more than expected based on the increase in dose; however, oral clearance (CL/F) and apparent volume of distribution (Vd/F) of trifluridine were generally constant at the dose range of 20 to 35mg/m^2. As for the other exposure parameters of trifluridine and tipiracil hydrochloride, those appeared to be dose proportional.

Time dependency

In the pharmacokinetic (PK) analyses of the multiple dose administration of Lonsurf (35 mg/m^2/dose, twice daily for 5 days a week with 2 days rest for 2 weeks followed by a 14-day rest, repeated every 4 weeks), trifluridine area under the concentration-time curve from time 0 to the last measurable concentration (AUC_{0-last}) was approximately 3-fold higher and maximum concentration ($C_{max)}$ was approximately 2-fold higher after multiple dose administration (Day 12 of Cycle 1) of Lonsurf than after single-dose (Day 1 of Cycle 1) (see section 5.2 of the SmPC).

There was no indication of further accumulation of trifluridine with successive cycles of TAS-102 administration (i.e. Day 12 of Cycle 2 and of Cycle 3 compared to that of Cycle 1).

The AUC for FTY was also increased (1.5-fold) after multiple dosing of TAS-102 compared to Day 1 in studies TPU-TAS-102-102, TPU-TAS-102-103 but not in Study J001-10040010; C_{max} values for FTY were similar after single and multiple dosing. Elimination half-life of FTY was increased following multiple dosing. On Day 1, the t1/2 ranged from 1.5 to 1.8 hours on average, and, on Day 12, the t1/2 ranged from 4.1 to 7.3 hours on average.

For tipiracil, AUC, and C_{max} were similar after single and multiple dosing of TAS-102. There was no accumulation for tipiracil hydrochloride, and no further accumulation of trifluridine with successive cycles (Day 12 of Cycles 2 and 3) of administration of Lonsurf.

Following multiple doses of Lonsurf (35 mg/m^2/dose twice daily) in patients with advanced solid tumours, the mean times to peak plasma concentrations (t_{max}) of trifluridine and tipiracil hydrochloride were around 2 hours

and 3 hours, respectively.

Endogenous thymidine exposure increased considerably by TAS-102 35 mg/m^2; plasma concentrations increased from 2 ng/ml to 97 ng/ml.

Intrasubject variability

Study TPU-TAS-102-104 was a partial replicate design study, allowing for intra-subject variability estimation. There is a considerable intersubject variability for both trifluridine and tipiracil. The intra-subject variability, however, is low to moderate for trifluridine AUC 16.4% and C_{max} 25.4%, respectively, while the intra-subject variability of tipiracil is moderate to high 28.9% for AUC and 36% for C_{max}.

Target populations

Pharmacokinetic parameters CL/F and Vd/F estimated by popPK analysis were in agreement with the pharmacokinetic parameters determined by non-compartmental analysis in patients with solid tumours. Exposure of trifluridine and tipiracil in patients with CRC has been determined in the phase 3 study RESOURSE by means of popPK analysis.

Special populations

Population PK analysis was conducted to evaluate intrinsic and extrinsic factors that may influence trifluridine and tipiracil exposure. The comparable exposure of trifluridine and tipiracil in patients with different BSA supports TAS-102 dosing based on BSA. In addition, creatinine clearance was a significant covariate for CL/F of trifluridine and tipiracil, and serum albumin was a significant covariate for CL/F of trifluridine. Other covariates tested such as age, gender, race, hepatic function parameters, and concomitant administration of OCT2 inhibitor were not significant covariates for either trifluridine or tipiracil PK parameters.

Impaired renal function

No formal renal impairment study has been conducted for Lonsurf. Based on a population PK analysis, the exposure of Lonsurf in patients with mild renal impairment (CrCl = 60 to 89 mL/min) was similar to those in patients with normal renal function (CrCl ≥ 90 mL/min). A higher exposure of Lonsurf was observed in moderate renal impairment (CrCl = 30 to 59 mL/min). Estimated (CrCl) was a significant covariate for CL/F in both final models of trifluridine and tipiracil hydrochloride. The mean relative ratio of AUC in patients with mild (n=38) and moderate (n=16) renal impairment compared to patients with normal renal function (n=84) were 1.31 and 1.43 for trifluridine, respectively, and 1.34 and 1.65 for tipiracil hydrochloride, respectively. The PK of trifluridine and tipiracil hydrochloride have not been studied in patients with severe renal impairment or end-stage renal disease (see section 5.2 of the SmPC).

Impaired hepatic function

No formal hepatic impairment study has been conducted for Lonsurf. Based on the population PK analysis, liver function parameters including alkaline phosphatase (ALP, 36-2322 U/L), aspartate aminotransferase (AST, 11-197 U/L), alanine aminotransferase (ALT, 5-182 U/L) , and total bilirubin (0.17-3.20 mg/dL) were not significant covariates for PK parameters of either trifluridine or tipiracil hydrochloride. The PK of trifluridine and tipiracil hydrochloride have not been studied in patients with moderate or severe hepatic impairment (NCI Criteria Group C and D). Serum albumin was found to significantly affect trifluridine clearance, with a negative correlation. For low albumin values ranging from 2.2 to 3.5 g/dL, the corresponding clearance values range from 4.2 to 3.1 L/h (see sections 4.4 and 5.2 of the SmPC).

Body weight

The comparable exposure of trifluridine and tipiracil in patients with different BSA supports TAS-102 dosing based on BSA.

In relation with age, number of patients ≥65 years of age included in population PK analysis should be broken down by the following ranges of age: 65-74, 75-84 and >85.

Age

The age of the patients ranged from 33 to 82 years old in the dataset analysed. Age was not a significant covariate for PK parameters of either trifluridine or tipiracil. Therefore, the PK of trifluridine and tipiracil are not expected to be affected by age.

Table 28: Number of elderly patients in TAS-102 PK studies

PK Trials	Age: 65-74 Older subjects /Total (%)	Age: 75-84 Older subjects /Total (%)	Age: 85+ Older subjects /Total (%)
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%)

Pharmacokinetic interaction studies

No dedicated in vivo drug interaction studies were conducted.

In vitro studies with human biomaterials showed no evidence that trifluridine and tipiracil are metabolized by the CYP enzymes tested. Neither trifluridine, FTY, nor tipiracil had an inhibitory or inducing effect on CYP suggesting that neither trifluridine, FTY, nor tipiracil would cause, or be affected by, a CYP-mediated drug interaction. The concentration of tipiracil in the induction study was too low to investigate the potential induction in intestinal cells. Potential induction of intestinal, renal and hepatic CYP3A4 by tipiracil relevant concentrations should be investigated.

Trifluridine seems to be no substrate for OATP1B1, OATP1B3, P-glycoprotein, BCRP. In vitro studies indicated that trifluridine is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2. Tipiracil was a substrate for OCT2 and MATE1 but not for OAT1, OAT3, P-glycoprotein, and BCRP.

Although tipiracil is also an in vitro inhibitor of OCT2, it is not considered to be an in vivo inhibitor, due to the relative high inhibition constant compared to the in vivo exposure to tipiracil.

2.4.3. Pharmacodynamics

Mechanism of action

Trifluridine is an antineoplastic thymidine-based nucleoside analogue, which is incorporated into deoxyribonucleic acid (DNA) in tumour cells following phosphorylation by thymidine kinase 1. TAS-102 demonstrated antitumour activity against both 5-FU sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of TAS-102 against several human tumour xenografts correlated with the amount of trifluridine incorporated into DNA, confirming this as the primary mechanism of action. These data provide support for rationale of treatment of patients with metastatic CRC with TAS-102 after initial treatment with conventional fluoropyrimidines.

Tipiracil inhibits degradation of trifluridine by inhibiting thymidine phosphorylase (thymidine phosphorylase), thus increasing systemic exposure to trifluridine when trifluridine and tipiracil are given together. Co-administration of tipiracil resulted in a 37-fold increase in trifluridine exposure

Primary and Secondary pharmacology

Biomarkers

In RECOURSE, patients were stratified for KRAS status. BRAF status was reported when status was available. No biomarker analysis was planned for RECOURSE.

Exposure-effect relationship

Specific dose-response and blood level-response analyses of efficacy with TAS-102 have not been completed. A PK/PD analysis of data obtained in the pivotal Phase 3 study (TPU-TAS-102-301; RECOURSE) was submitted with the response to D120 LoQ.

This report evaluated the PKPD data collected during the RECOURSE trial. A total of 138/534 (25.8%) patients in the TAS-102 group had evaluable parameters (estimated trifluridine AUC and tipiracil AUC) and are included in the PK/PD analysis. Patients in the TAS-102 treatment group who participated in the optional PK assessment were categorised into two groups, a high-exposure group (>median) and a low-exposure group (≤median) based on median AUC values of trifluridine (43.51 hr*µg/mL) and tipiracil (0.65 hr*µg/mL).

Patient demographics and baseline characteristics for most parameters were comparable for the 2 groups and within the patient subgroups defined according to median trifluridine or tipiracil AUCs. In the trifluridine and tipiracil high AUC groups, there were more patients ≥65 years of age (trifluridine, 50.7%; tipiracil, 46.4%) and more patients with mild to moderate renal impairment at baseline based on creatinine clearance (trifluridine, 56.5%; tipiracil, 56.5%) and baseline eGFR (trifluridine, 49.3%; tipiracil, 50.7%) compared to the respective low AUC group with baseline based on creatinine clearance (trifluridine, 21.7%; tipiracil, 21.7%) and baseline eGFR (trifluridine, 21.7%; tipiracil, 20.3%). In the trifluridine high AUC subgroup there were more females 47.8% vs the low AUC subgroup 26.1%, while there was no difference for the tipiracil high/low subgroups 36.2% vs. 37.7%.

The subpopulation included in the PKPD analysis is not fully representative for the TAS-102 treated subgroup as overall survival seems higher in in this PKPD population vs. TAS-102 ITT population in RECOURSE (8.9 vs 7.1 months and HR 0.53 vs. 0.68). This trend was observed also for radiologic PFS as the TAS-102 PK/PD group median PFS (3.3 months) was longer for TAS-102 and placebo (2.0 and 1.7 months, respectively). Therefore, the data should be interpreted with caution.

In the trifluridine group, OS appeared more favourable in the high AUC group compared to the low AUC group

(HR, 0.72 [CI: 0.46, 1.11]) and the associated OS medians were 9.3 vs. 8.1 months, respectively. PFS also appeared more favourable in the high AUC group compared to the low AUC group (HR, 0.82 [CI: 0.57, 1.18]) and the associated PFS medians were 3.7 vs. 2.0 months, respectively.

In the tipiracil group, the direction of the OS effect was not as pronounced, but was in favour of the low tipiracil AUC group (HR, 1.09 [CI: 0.70, 1.69]) and median OS was 7.8 months in the high AUC group compared with 9.2 months in the low AUC group. No specific pattern emerged in the PFS results with a HR 0.97, [CI: 0.67, 1.41] and median PFS of 2.0 months in the high AUC group compared to 3.7 months in the low AUC group.

Consistent with the OS and PFS results for the overall PK/PD Population, all AUC groups performed better than placebo throughout the follow-up period.

QTc prolongation

Pre-clinical studies indicate that trifluridine and tipiracil have no effect on hERG channel. Also other fluoropyrimidines are not known to prolongate QTc prolongation.

Based on the results of the linear model for the relationship between plasma trifluridine, FTY, and tipiracil concentrations and the placebo-adjusted baseline-subtracted QTc intervals, no concentration dependent QT-prolonging effect was observed.

Haematologic toxicities

In the dose finding study J001-10040010, Cmax and AUC of trifluridine were associated with haematologic toxicities. In RECOURSE study, PKPD analysis indicated that the incidence of Grade ≥3 neutropenia and any Grade ≥3 drug related AE was higher (>10%) in the trifluridine high AUC group compared with the low AUC group. Any dose reduction was higher in the trifluridine high AUC group (23%) compared with the low AUC group (9%). However, no apparent difference was seen between the tipiracil high AUC group and the low AUC group.

Pharmacodynamic interactions

Trifluridine, like other thymidine analogues such as the anti-viral agent AZT, is phosphorylated by thymidine kinase prior to incorporation into DNA. Attenuation of the inhibitory effect of trifluridine on tumour cell proliferation in the presence of AZT was considered due to competition for thymidine kinase in vitro (Study No. 03-13-004). However, treatment with TAS-102 in combination with AZT in rats did not influence the toxicity relative to TAS-102 alone (Study No.13CC20).

2.4.4. Discussion on clinical pharmacology

Trifluridine is an antineoplastic thymidine-based nucleoside analogue, which is incorporated into deoxyribonucleic acid (DNA) in tumour cells following phosphorylation by thymidine kinase 1. TAS-102 demonstrated antitumour activity against both 5-FU sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of TAS-102 against several human tumour xenografts correlated with the amount of trifluridine incorporated into DNA, confirming this as the primary mechanism of action. These data provided support for rationale of treatment of patients with metastatic CRC with TAS-102 after initial treatment with conventional fluoropyrimidines.

In the pivotal study RECOURSE, patients were stratified for KRAS status. No further biomarker analysis was planned for RECOURSE. Relation of expression of thymidine phosphorylase and thymidine kinase, two enzymes known to play an essential role in the mechanism of action of trifluridine, with efficacy has not been discussed. In cell lines development of resistance to trifluridine involved decreased activity of thymidine kinase 1 and

nucleoside transporter (Temmink 2010). In xenografts, antitumor activity of TAS-102 was best related to the thymidine kinase and thymidine phosphorylase ratio (Emura 2004). Furthermore, deficient mismatch repair enzyme status (dMMR) is associated with sensitivity to fluoropyrimidine-based adjuvant treatment of CRC (Sargent 2010) and, given the mechanism of action of trifluridine, MMR status could be an important marker for TAS-102 treatment. MSI status and TK1 as possible biomarkers will be further explored in a selected Japanese subpopulation from the phase III RECOURSE study.

The oral bioavailability of trifluridine is low due to degradation by thymidine phosphorylase, therefore monotherapy with trifluridine is not feasible. Tipiracil prevents degradation of trifluridine by inhibiting thymidine phosphorylase (thymidine phosphorylase), thus increasing systemic exposure to trifluridine when trifluridine and tipiracil are given together. Co-administration of tipiracil resulted in a 37-fold increase in trifluridine exposure. This demonstrates the rationale for addition of tipiracil, in the combination of trifluridine and tipiracil (TAS-102).

Trifluridine and tipiracil have high solubility and low/moderate permeability characteristics. Permeability of trifluridine and tipiracil is the rate limiting step for absorption.

The to-be marketed formulation has not been used in clinical studies. The composition of the to-be marketed formulation is identical to the late formulation except for imprinting. No bioequivalence study is considered necessary for the to-be market formulation, because trifluridine and tipiracil are BCS class III compounds, the composition of the tablets was identical and dissolution of all formulations was very fast at all pH tested, i.e. dissolution ≥85% at 15min.

Selection of the tipiracil dose in TAS-102 was based on a single dose finding study in 4 male cynomolgous monkeys 4 using one trifluridine dose with 3 different tipiracil doses (molar ratio trifluridine:tipiracil 1:0.2, 1:0.5 and 1:1). All three doses of tipiracil greatly enhanced the oral bioavailability of trifluridine in monkeys. The applicant did not provide in vitro data on the inhibition of thymidine phosphorylase by tipiracil to support dosing based on molar ratio rather than using a high flat tipiracil dose that maximally inhibits thymidine phosphorylase. No studies in humans were conducted to confirm the appropriate dose of tipiracil. Although study TAS-102-102 showed that bioavailability of trifluridine was greatly increased in presence of tipiracil a more than dose proportional increase in trifluridine was observed over the dose range 15-35 mg/m^2 suggesting that inhibition of thymidine phosphorylase by tipiracil is not maximal. tipiracil is an competitive inhibitor of TPase with a Ki of 5 ng/ml. Because tipiracil was shown to be a competitive inhibitor of TPase, the dose administration of tipiracil as a molar ratio to trifluridine is considered acceptable. However, it was shown that there is a positive correlation between trifluridine and tipiracil exposure. The estimated 1.5-2 fold higher trifluridine exposure as results of a higher tipiracil exposure is small compared to the 37-fold increase in exposure of trifluridine as result of co-administration with tipiracil. Therefore, inhibition of TPase by tipiracil is probably near maximal.

The clinical dose and dosing interval of Lonsurf has been supported by non-clinical studies but final dose and dosing interval i.e. 35 mg/m^2 bid for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks, has been selected based on tolerability in patients with solid tumours and CRC. Given the high number of dose delay in the phase 3 study and the two different MTD determined, the applicant was requested to discuss the selected dose and dosing interval further (see clinical efficacy part). Exposure effect relationship indicated that higher exposure to trifluridine was associated with longer overall survival and greater risk of safety events, but exposure to tipiracil was not.

The applicant claims that 80 mg/dose should not be exceeded as included in the protocol for RECOURSE study. However ASCO guideline (2012) recommends the use of actual body weight to calculate appropriate dose of chemotherapy drugs for obese patients. Additional PopPK analysis indicated that capping of the dose to 80 mg in the current dosing regimen is unlikely to result in underexposure of FTD in obese adult patients.

The applicant recommended TAS-102 to be administered in a fed state because C_{max} and AUC of trifluridine were associated with haematologic toxicities (Study J001-100400100) and C_{max} of trifluridine was lower under fed conditions. When taken within one hour after completing a meal, trifluridine and tipiracil are rapidly absorbed with T_{max} of around 2 hours and 3 hours, respectively. After peak concentrations are reached, trifluridine and tipiracil plasma concentrations declined rapidly with an elimination half-life of 2 hours. In the clinical dose range 20-35 mg/m2, trifluridine pharmacokinetics can be considered dose proportional. The AUC of trifluridine was not decreased after a meal and, therefore, the applicant considered it unlikely that efficacy is affected when TAS-102 is administered with a meal. The dosing recommendation in the SmPC to take TAS-102 after a meal reflect the conditions it has been administered in the pivotal and most other clinical studies.

Exposure of trifluridine was 2 to 3-fold higher following multiple dosing (Day 12 cycle 1) compared to single dose administration of TAS-102. This is unexpected given the short elimination half-life of trifluridine 2 h and the twice daily dosing. There was no indication of further accumulation of trifluridine with successive cycles of TAS-102 administration (i.e. Day 12 of Cycle 2 and of Cycle 3 compared to that of Cycle 1). Pharmacokinetics of tipiracil were dose proportional and exposure was similar after single and multiple dosing of TAS-102. Therefore a more profound inhibition of thymidine phosphorylase by tipiracil following multiple dosing is not expected. Reasons for the time dependent pharmacokinetics of trifluridine is not known. Because maximal accumulation was reached by the end of the first cycle and did not further increase in following cycles and the accumulation was consistent among patients, the accumulation of trifluridine after repeated administration is considered not to be a safety or efficacy risk of TAS-102.

Major elimination pathway for trifluridine seems degradation by thymidine phosphorylase to metabolite FTY. FTY does not show anti-tumour activity. Of the administered dose, 55% of the administered dose was excreted as trifluridine related compounds but only a small fraction of the administered dose of TAS-102 was excreted as unchanged trifluridine (1.5 and 3.7%). Nevertheless, trifluridine exposure was approximately 50% higher in patients with moderate renal impairment compared to patients with normal renal function. Trifluridine exposure was correlated with tipiracil exposure. Therefore, the increased trifluridine exposure in patients with moderate renal impairment might (in part) be due to the higher tipiracil exposure in patients with moderate renal impairment.

Excretion of tipiracil in the urine is probably the primary elimination pathway of tipiracil but 17% of the administered dose was excreted as 6-HMU metabolite in faeces, indicating a secondary elimination pathway. 27% - 29% of the administered dose of tipiracil was excreted in its unchanged form. Renal clearance of tipiracil was 293 ml/min, exceeding the glomerular filtration rate suggesting a transporter mediated excretion of tipiracil in the urine. Tipiracil is a substrate for OCT2 and MATE1. These transporters may be involved in the excretion of tipiracil in urine.

In the popPK analysis, no patients with severe renal impairment and moderate or severe hepatic impairment were included. Lack of efficacy and safety data in patients with severe renal impairment and moderate and severe hepatic impairment has been acknowledged in the SmPC. Trifluridine exposure was approximately 50% higher in patients with moderate renal impairment compared to patients with normal renal function. Patients with moderate renal impairment experienced more adverse events and should be more often monitored for haematological toxicities (see section 4.4 of the SmPC). The applicant will conduct a renal impairment study (TPU-TAS-102-107), which results will be available by December 2017. In addition, a formal hepatic impairment study is considered necessary. The applicant will conduct a hepatic impairment study (TPU-TAS-102-106) and submit the results by December 2017 (see RMP).

There was a negative correlation between serum albumin and CL/F of trifluridine. In vitro studies indicated that protein binding was not concentration dependent. Ex vivo protein binding in plasma from subjects in the renal and hepatic impairment studies may further elucidate this issue.

No adjustment of the starting dose is required on the basis of patient's race.

The influence of gastrectomy on PK parameters could not be examined in the population PK analysis because there were few patients who had undergone gastrectomy (1% of overall). This is adequately reflected in section 5.2 of the SmPC.

Potential interactions involving CYP450 enzymes is considered low as trifluridine and tipiracil are no substrate, inhibitor or inducer of CYP450 enzymes. However, inductive effect of tipiracil on human CYP isoforms cannot be excluded.

In vitro transport studies indicated that trifluridine and tipiracil are no substrates for P-glycoprotein and BCRP and trifluridine is not likely to be a substrate for OATP1B1. OATP1B3, OAT1, and OAT3 transporters.

Trifluridine is intracellularly activated by thymidine kinase. Nucleoside transporters mediate the uptake of trifluridine into the cells (Takahashi 2015, Sakamoto 2015) In vitro studies have indicated that expression of thymidine kinase and expression of nucleoside transporters may be involved in resistance to trifluridine. Effect of polymorphisms on trifluridine function is not known but for gemcitabine, expression of hENT1 and polymorphism of hENT1 has been associated with efficacy and toxicity of gemcitabine (Tanaka et al 2010).

Trifluridine, like other thymidine analogues such as the anti-viral agent AZT, is phosphorylated by thymidine kinase prior to incorporation into DNA. Caution is required when using medicinal products that are human thymidine kinase substrates, e.g., zidovudine. Such medicinal products, if used concomitantly with Lonsurf, may compete with the effector, trifluridine, for activation via thymidine kinases. Therefore, when using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir (see sections 4.5 and 5.1 of the SmPC).

Study J001-100400100 showed that endogenous thymidine exposure increased considerably by Lonsurf 35 mg/m^2 from 2 to 97 ng/ml. However, the increased concentration of thymidine following multiple dosing of Lonsurf is still much lower than the plasma concentrations of trifluridine C_{max} 2381 ng/mL, therefore, competition for phosphorylation by thymidine kinase 1 or nucleoside transporters seems unlikely.

As trifluridine was shown to be a substrate for the nucleoside transporters CNT1, ENT1 and ENT2, caution is required when using medicinal products that interact with these transporters.

No dedicated in vivo drug interaction studies were conducted. Tipiracil hydrochloride was a substrate for OCT2 and MATE1, therefore, the concentration might be increased when Lonsurf is administered concomitantly with inhibitors of OCT2 or MATE1.

It is unknown whether Lonsurf may reduce the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptive must also use a barrier contraceptive method (see section 4.6 of the SmPC).

The efficacy and safety of Lonsurf was compared between a high-exposure group (>median) and a low-exposure group (≤median) based on the median AUC value of trifluridine. OS appeared more favourable in the high AUC group compared to the low AUC group (median OS of 9.3 vs. 8.1 months, respectively). All AUC groups performed better than placebo throughout the follow-up period. The incidences of Grade ≥3 neutropenia were higher in the high-trifluridine AUC group (47.8%) compared with the low-trifluridine AUC group (30.4%).

2.4.5. Conclusions on clinical pharmacology

The pharmacology package supporting the pharmacokinetic & pharmacodynamic characterisation of trifluridine and tipiracil is comprehensive and in general well executed. Studies in patients with renal and hepatic impaired function are ongoing and results are awaited (see RMP). Induction of CYP enzymes by tipiracil cannot yet be excluded and the applicant is recommended to conduct an additional in vitro CYP induction study using the appropriate concentration of tipiracil. In addition, the applicant is recommended to further evaluate biomarkers involved in the mechanism of action of trifluridine.

2.5. Clinical efficacy

This application is supported by the results of one pivotal phase III TPU-TAS-102-301 RECOURSE study and supportive data from a Phase II trial conducted in Japan (Study J003-10040030).

2.5.1. Dose response study(ies)

A series of initial dose-finding Phase 1 studies were conducted in the US in patients with solid tumours. Based on preclinical findings (Study M96-029), these studies used daily dosing of TAS-102 in order to facilitate FTD incorporation into tumour cells. In the first 3 studies initiated (Studies TAS102-9801, TAS102-9802, and TAS102-9803), TAS-102 was administered once daily (QD) using various dosing schedules of 3- or 4-week cycles. The initial starting dose in the first human study (TAS102-9801) was 100 mg/m^2/day, which was 1/3 of the toxic low dose in a 4-week toxicity study in monkeys. The results of these studies indicated that TAS-102 was better tolerated when administered for 5 consecutive days rather than for 14 consecutive days, and a dose regimen of 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks was determined to be the optimal dosing regimen.

While these initial 3 studies were on-going, results of non-clinical studies became available that demonstrated significantly greater tumour reduction in mice following BID dosing compared with QD dosing. Therefore, 2 additional studies were initiated to evaluate BID and three times daily (TID) dosing (Studies TAS102-9804 and TAS102-9805, respectively) 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 maximum tolerated dose (MTD) was 50 mg/m^2/day, while in study TAS102-9805, which was conducted in a patient population of primarily mCRC patients, the MTD was 70 mg/m^2/day.

In a subsequent Phase 1 dose-finding study conducted in Japan (Study J001-10040010), a TAS-102 regimen of 35 mg/m^2 BID (70 mg/m^2/day) administered 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, was well tolerated in patients with advanced solid tumours. The efficacy and safety of this regimen was established in the Japanese Phase 2 study in patients with mCRC (Study J003-10040030). The tolerability of this regimen in Western patients with refractory metastatic colorectal cancer was confirmed in a Phase 1 dose-finding study conducted in the US (Study TPU-TAS-102-101). Therefore, this regimen was selected for evaluation in the pivotal, global, Phase 3 study (RECOURSE).

Selection of the tipiracil dose in TAS-102 was based on a single dose finding study in 4 male cynomolgous monkeys 4 using one trifluridine dose with 3 different tipiracil doses (molar ratio trifluridine:tipiracil 1:0.2, 1:0.5 and 1:1). All three doses of tipiracil greatly enhanced the oral bioavailability of trifluridine in monkeys. Because the difference in AUC of trifluridine was not statistically significant different for 1:0.5 and 1:1 ratio, TAS-102 was optimized at a molar ratio of 1:0.5 (trifluridine:tipiracil).

2.5.2. Main study

Study TPU-TAS-102-301 (RECOURSE): Randomised, double-blind, phase 3 study of TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer refractory to standard chemotherapies.

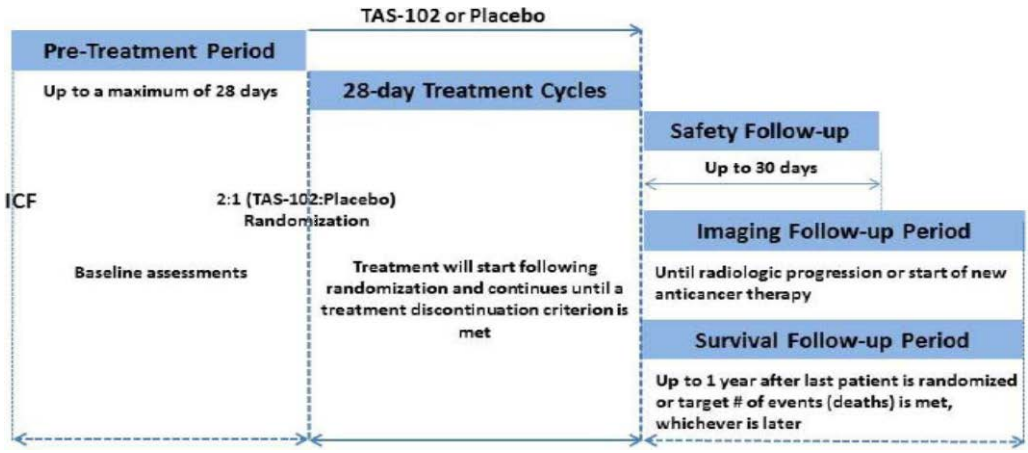


Figure 8: Study Design - RECOURSE

Methods

Study Participants

Key inclusion criteria

Male and female patients age 18 years or older with definitive histologically or cytologically confirmed adenocarcinoma of the colon or rectum with KRAS status determined (mutant or wild-type), and an Eastern Cooperative Group (ECOG) performance status of 0 or 1.

Patients must have received at least 2 prior regimens of standard chemotherapies for metastatic colorectal cancer and were refractory to or failing those chemotherapies as follows:

- 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)
  - At least one of the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients.
- Patients who had progressed based on imaging during or within 3 months of the last administration of each of the standard chemotherapies.
- Patients who had withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease were also eligible to enter the study.
- Patients who had received adjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count the adjuvant therapy as one regimen of chemotherapy.
- Patients who had adequate organ function as defined by pre-define laboratory values obtained within 7 days prior to study drug administration on Day 1 of Cycle 1.

Key exclusion criteria

Subjects who met any of the following main exclusion criteria were to be excluded from the study:

- Had a serious illness or medical condition(s), such as:
  - Other concurrently active
  - Known brain metastasis or leptomeningeal metastasis.
  - Active infection (ie, body temperature ≥38°C due to infection).
  - Ascites, pleural effusion or pericardial fluid requiring drainage in last 4 weeks.
  - Intestinal obstruction, pulmonary fibrosis, renal failure, liver failure, or cerebrovascular disorder.
  - Uncontrolled diabetes.
  - Myocardial infarction within the last 12 months, severe/unstable angina, symptomatic congestive heart failure New York Heart Association (NYHA) class III or IV.
  - Gastrointestinal hemorrhage.
  - Known HIV) or AIDS-related illness, or hepatitis B or C.
  - Patients with autoimmune disorders or history of organ transplantation who required immunosuppressive therapy.
  - Psychiatric disease that may have increased the risk associated with study participation or study drug administration, or may have interfered with the interpretation of study results.
- Had treatment with any of the following within the specified time frame prior to study drug administration:

  a. Major surgery within prior 4 weeks (the surgical incision should be fully healed prior to study drug administration).

  b. Any anticancer therapy within prior 3 weeks (except for bevacizumab within prior 4 weeks).

  c. Extended field radiation within prior 4 weeks or limited field radiation within prior 2 weeks.

  d. Any investigational agent received within prior 4 weeks.

- Had received TAS-102.
- Had unresolved toxicity of greater than or equal to Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).
- Was a pregnant or lactating female.
- Was inappropriate for entry into this study in the judgment of the Investigator.

Treatments

Patients received TAS-102 35 mg/m^2/dose or placebo, administered orally BID (after morning and evening meals) for 5 days a week and 2 days of rest (during weeks 1 and 2), followed by a 14-day rest (1 treatment cycle), repeated every 4 weeks.

Method of Assigning Subjects to Treatment

Once patient confirmation of eligibility and the criteria for randomisation had been met, patients were centrally randomised in a 2:1 ratio to TAS-102 or placebo via an Interactive Voice/Web Response System (IWRS) based on a dynamic allocation method (biased coin). The IWRS assigned kit numbers corresponding to the patient's treatment assignment and informed the study site user of the kit number that had been assigned to the patient for the dispensing of study drug.

Duration

Patients received study medication until any of the discontinuation criteria were met:

- Patient request at any time irrespective of the reason;
- RECIST-defined or clinical disease progression;
- Patient experienced an irreversible, treatment-related, Grade 4, clinically relevant, non-haematologic event;
- Unacceptable toxicity, or change in underlying condition such that the patient could no longer tolerate therapy;
- Physician's decision (includen the need for other anticancer treatments);
- Pregnancy.

Dose reductions/Interruptions

Study medication dose reductions were allowed in the case of toxicity. A maximum of 3 dose reductions of study medication were permitted, in 5 mg/m^2 steps, to a minimum dose of 20 mg/m2 (40 mg/m2/day). Dose escalations (on a "mg/m^2" basis) were not permitted at any time.

Objectives

The primary objective of the RECOURSE trial was to compare the overall survival (OS) for TAS-102 + best supportive care (BSC) (experimental arm) with placebo + BSC (control arm) in patients with refractory metastatic colorectal cancer.

Secondary objectives included the comparison of TAS-102 and placebo for Progression-free survival (PFS); Safety and tolerability.

Outcomes/endpoints

Primary endpoint:

Overall survival was defined as the time [in months] from the date of randomisation to the date of death for each patient in the ITT population.

Secondary endpoint:

- 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.

- 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.

- Overall response rate was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR) with no confirmatory scan required. The assessment of ORR was based on Investigator review of radiologic images following RECIST criteria (version 1.1, 2009) 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.

- Disease control rate was defined as the proportion of patients with a best overall response of CR, PR, or SD.

- Duration of response, 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.

Sample size

The study was designed to detect with 90% power a hazard ratio for OS of 0.75 (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 of 2:1 (TAS-102: placebo) of 800 patients, a target of 571 events (deaths) was required for the primary analysis.

Based on these design operating characteristics and assuming a median survival time of approximately 5 months in the control arm, the primary analysis target events milestone was projected to be reached approximately 5 months after the last patient was randomised in the study. 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 3 cetuximab study. The estimate was rounded to 5 months to reflect a higher control median in the Japanese population, as observed in the Phase 2 study (J003-10040030).

Randomisation

Patients were randomised (2:1) to receive TAS-102 or placebo. In order to ensure comparability of the treatment groups, patients were to be stratified by KRAS status (wild-type, mutant), time since diagnosis of metastasis (<18 months, ≥18 months), and geographic region (Region 1: Asia [Japan]; Region 2: Western [Australia, Europe, US]).

Blinding (masking)

This was a double-blind study. TAS-102 tablets of each of the strengths and the corresponding placebo tablets were identical in appearance and were packaged in identical containers. During the conduct of the study, the treatment assignment was unknown to all patients, investigators, and ancillary study personnel at each study site.

Statistical methods

Analysis sets

The primary population for the efficacy analysis was the ITT population, which was defined as all randomized patients, independently on whether they received or not study medication.

The population for safety analysis comprised all patients who received at least 1 dose of study medication.

Analysis methods

The difference in OS between the two treatment arms was assessed in the ITT population using the stratified log-rank test and the HR was estimated using a Cox proportional hazards (CPH) model including treatment and the 3 stratification factors in the model. Overall survival for each arm was summarised using Kaplan Meier curves and was further characterised in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% confidence intervals (CIs) for the estimates.

The primary analysis of OS includes 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.

For analyses of PFS, the two treatment groups were compared using a log-rank test stratified by the same stratification factors as used in the analyses of the primary endpoint. The HR (TAS-102 plus BSC group/placebo plus BSC group) and 95% confidence interval were provided. KM estimates and KM curves were also presented for each treatment group. ORR and DCR were compared between treatments. The differences in ORR between

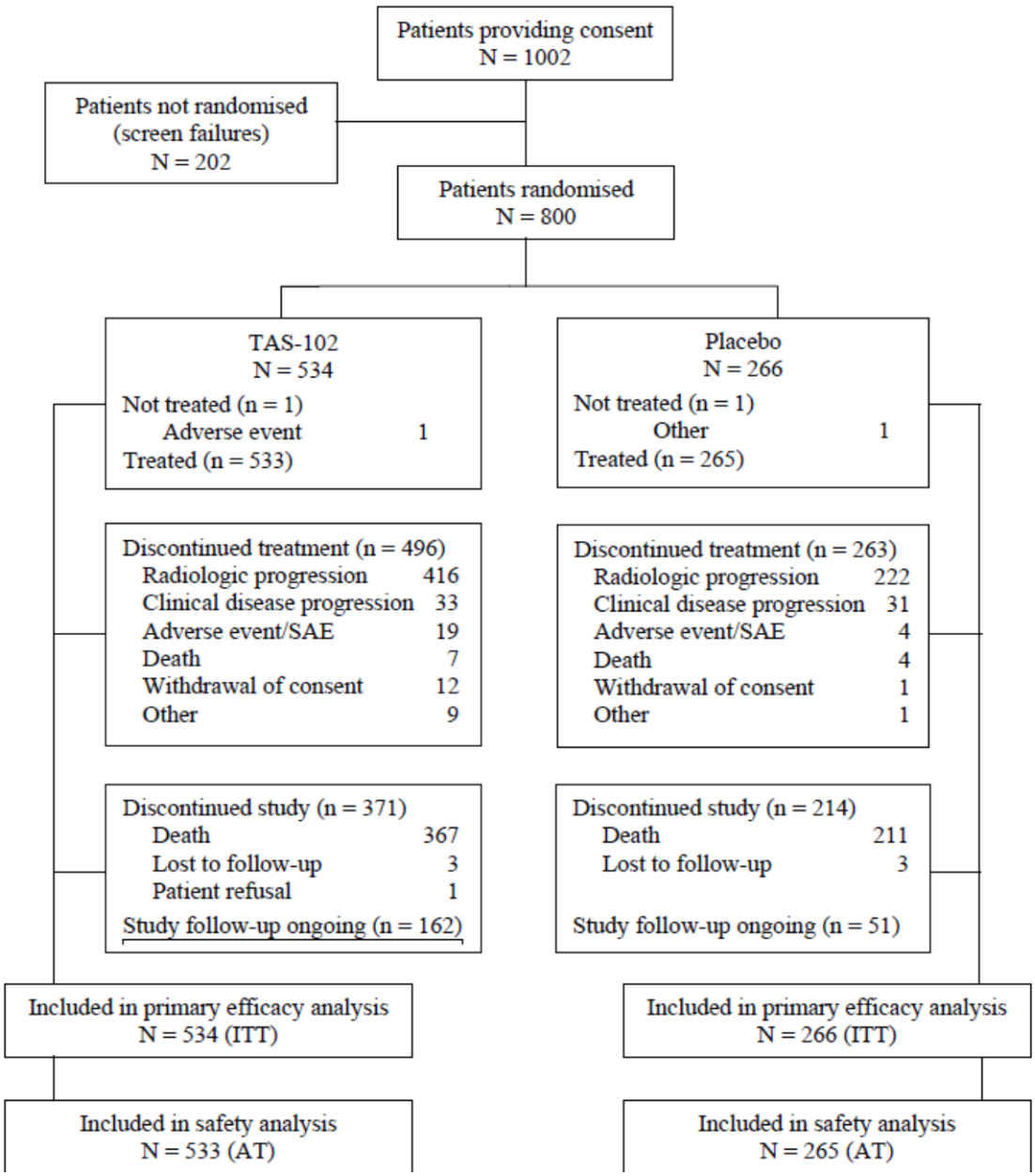
the TAS-102 and placebo group and the corresponding 95% confidence intervals were also calculated. Several sensitivity analyses for PFS have been performed.

Interim analyses

No interim analyses for efficacy or futility were planned or performed during this study.

Results

Participant flow



Recruitment

A total of 800 patients were randomised (2:1) into the study (ITT population), 534 in the TAS-102 group and

266 in the placebo group, consistent with the planned 2:1 randomization. The study was conducted in a total of 101 sites in 13 countries (number of sites): 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).

Conduct of the study

The original study protocol dated 23 February 2010 was subsequently amended 8 times, including 3 worldwide amendments and 5 country-specific amendments.

Amendment 1 (dated 28 March 2012) essentially clarified inclusion/exclusion criteria, and clarification of stratification variables

Amendment 2 (dated 22 April 2012) essentially was implemented to remove carbon dioxide measurements from clinical chemistry tests

Amendment 3 (dated 13 November 2012) essentially was implemented for clarification of end of study treatment, exclusion criteria and to exclude interacting thymidine analogous during study treatment.

Baseline data

Table 29: Demographic and Other Baseline Characteristics (ITT Population) – RECOURSE study

Parameter	TAS-102 (N=534)	Placebo (N=266)	Total (N=800)
Gender, n (%)			
Male	326 (61.0)	165 (62.0)	491 (61.4)
Female	208 (39.0)	101 (38.0)	309 (38.6)
Age (years)			
Mean (SD)	61.5 (10.21)	61.5 (10.51)	61.5 (10.30)
Median	63.0	63.0	63.0
Min, Max	27, 82	27, 82	27, 82
Age category (years), n (%)			
<65	300 (56.2)	148 (55.6)	448 (56.0)
≥65	234 (43.8)	118 (44.4)	352 (44.0)
65-<75	198 (37.1)	94 (35.3)	292 (36.5)
≥75	36 (6.7)	24 (9.0)	60 (7.5)
Race, n (%)			
Caucasian/White	306 (57.3)	155 (58.3)	461 (57.6)
Black/African American	4 (0.7)	5 (1.9)	9 (1.1)
Asian/Oriental	184 (34.5)	94 (35.3)	278 (34.8)
Not Collected	40 (7.5)	12 (4.5)	52 (6.5)
Body Surface Area (m^2)			
Mean (SD)	1.781 (0.2331)	1.790 (0.2198)	1.784 (0.2287)
Median	1.770	1.780	1.770
Min, Max	1.21, 2.43	1.28, 2.49	1.21, 2.49
ECOG Performance Status, n (%)			
0	301 (56.4)	147 (55.3)	448 (56.0)
1	233 (43.6)	119 (44.7)	352 (44.0)
KRAS Gene Type (based on IWRS), n (%)			
Wild-type	262 (49.1)	131 (49.2)	393 (49.1)
Mutant	272 (50.9)	135 (50.8)	407 (50.9)
Time Since Diagnosis of Metastasis (based on IWRS), n (%)			
<18 months	111 (20.8)	55 (20.7)	166 (20.8)
≥18 months	423 (79.2)	211 (79.3)	634 (79.3)
Baseline Renal Function, n (%)[a]			
Normal (CLcr ≥90 mL/min)	307 (57.5)	145 (54.5)	452 (56.5)
Mild Impairment (CLcr 60-89 mL/min)	178 (33.3)	91 (34.2)	269 (33.6)
Moderate Impairment (CLcr 30-59 mL/min)	47 (8.8)	27 (10.2)	74 (9.3)
Missing	2 (0.4)	3 (1.1)	5 (0.6)
Baseline eGFR, n (%)[b]			
Normal (eGFR ≥90 mL/min/1.73m^2)	335 (62.7)	160 (60.2)	495 (61.9)
Mild Impairment (eGFR 60-89 mL/min/1.73m^2)	153 (28.7)	82 (30.8)	235 (29.4)
Moderate Impairment (eGFR 30-59 mL/min/1.73m^2)	33 (6.2)	16 (6.0)	49 (6.1)
Missing	13 (2.4)	8 (3.0)	21 (2.6)

More patients with KRAS wild type (85.5%) were ≥18 months post time since diagnosis of metastases compared to patients with KRAS mutant tumours (73.2%) , consistent with the availability of EGFR-inhibitors for patients with KRAS wild-type tumours. ifteen percent of tumours harboured a BRAF wild type and in only 0.7% (TAS-102) and 1,5% (placebo) tumours had a BRAF mutation.

Table 30: Cancer Diagnosis (ITT Population) – RECOURSE study

Parameter	TAS-102 (N=534)	Placebo (N=266)	Total (N=800)
Location of Primary Tumour, n (%)			
Colon	338 (63.3)	161 (60.5)	499 (62.4)
Rectal	196 (36.7)	105 (39.5)	301 (37.6)
Time from Initial Diagnosis to Randomisation (months)			
n	533	266	799
Mean (SD)	44.1 (29.32)	45.5 (28.28)	44.6 (28.97)
Median	36.0	39.0	36.0
Min, Max	8, 184	8, 170	8, 184
Time from Confirmed Metastasis to Randomisation (months)			
n	534	266	800
Mean (SD)	36.0 (22.16)	37.3 (21.83)	36.4 (22.04)
Median	31.0	32.0	31.0
Min, Max	5, 172	8, 154	5, 172

Regarding prior systemic cancer therapy, both treatment groups were comparable with respect to prior systemic cancer therapies.

Table 31: Prior Cancer Therapies (ITT Population) – RECOURSE study

Parameter	Number (%) of Patients		
	TAS-102 (N=534)	Placebo (N=266)	Total (N=800)
Prior Surgery/Biopsy Related to Cancer, n (%)[a]			
Yes (excludes patients with biopsy only)	474 (88.8)	240 (90.2)	714 (89.3)
Primary	402 (75.3)	210 (78.9)	612 (76.5)
Resection Of Hepatic Mets	139 (26.0)	74 (27.8)	213 (26.6)
Resection Of Pulmonary Mets	46 (8.6)	31 (11.7)	77 (9.6)
Other	209 (39.1)	101 (38.0)	310 (38.8)
Biopsy	332 (62.2)	168 (63.2)	500 (62.5)
None	0	0	0
Prior Radiotherapy, n (%)[a]			
Yes	139 (26.0)	65 (24.4)	204 (25.5)
Palliative	67 (12.5)	37 (13.9)	104 (13.0)
Curative	84 (15.7)	33 (12.4)	117 (14.6)
No	393 (73.6)	198 (74.4)	591 (73.9)
All Prior Systemic Cancer Therapeutic Agents, n (%)[a,b,c]			
Bevacizumab	534 (100)	265 (99.6)	799 (99.9)
Cetuximab/Panitumumab	278 (52.1)	144 (54.1)	422 (52.8)
KRAS wild-type patients only (based on eCRF)	259 (99.6)[d]	133 (99.3)[e]	392 (99.5)[f]
Fluoropyrimidine	534 (100)	266 (100)	800 (100)
Irinotecan	534 (100)	266 (100)	800 (100)
Oxaliplatin	534 (100)	266 (100)	800 (100)
Regorafenib	91 (17.0)	53 (19.9)	144 (18.0)
Other	471 (88.2)	237 (89.1)	708 (88.5)
Intent of All Prior Systemic Cancer Therapy, n (%)[a]			
Neoadjuvant	69 (12.9)	30 (11.3)	99 (12.4)
Adjuvant	185 (34.6)	97 (36.5)	282 (35.3)
Metastatic	534 (100)	266 (100)	800 (100)
Total Number of Prior Regimens, n (%)[b]			
1	0	0	0
2	95 (17.8)	45 (16.9)	140 (17.5)
3	119 (22.3)	54 (20.3)	173 (21.6)
≥ 4	320 (59.9)	167 (62.8)	487 (60.9)
Total Number of Prior Regimens for Metastatic Cancer, n (%)			
1	15 (2.8)	9 (3.4)	24 (3.0)
2	123 (23.0)	59 (22.2)	182 (22.8)
3	154 (28.8)	68 (25.6)	222 (27.8)
≥ 4	242 (45.3)	130 (48.9)	372 (46.5)

[a] Patients counted in each applicable category.
[b] Includes neoadjuvant, adjuvant, metastatic.
[c] Fluoropyrimidine category includes fluorouracil, capecitabine, doxifluridine, S-1, tegafur and UFT.
[d] n=260 for KRAS wild-type patients (denominator for percentage).
[e] n=134 for KRAS wild-type patients (denominator for percentage).
[f] n=394 for KRAS wild-type patients (denominator for percentage).

The median number of prior lines of therapy for metastatic disease was 3. All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; and all but 1 patient had received bevacizumab. All but 2 patients with KRAS wild-type tumours had received panitumumab or cetuximab. The majority of patients (60.9%) had received ≥4 prior systemic cancer therapies. Sixty one percent (61%, N = 485) of all randomised patients received a fluoropyrimidine as part of their last treatment regimen prior to randomisation, of which 455 (94%) were refractory to the fluoropyrimidine at that time.

Post-study treatments

Post-treatment included use of regorafenib (Table 32) and was equally distributed between the TAS-102 and placebo groups. More than 40% of patients actually received post-study treatments.

Table 32: Post-study Anti-tumour Treatments Received After the End of the Treatment Period (ITT Population) – RECOURSE study

Treatment	Number (%) of Patients		
	TAS-102 (N=534)	Placebo (N=266)	Total (N=800)
Surgery	6 (1.1)[a]	5 (1.9)	11 (1.4)
Surgery or systemic anti-cancer therapy	224 (41.9)	118 (44.4)	342 (42.8)
Radiotherapy	0	0	0
Any systemic therapy	222 (41.6)	113 (42.5)	335 (41.9)
Number of regimens			
1	170 (31.8)	88 (33.1)	258 (32.3)
2	41 (7.7)	22 (8.3)	63 (7.9)
≥3	11 (2.1)	3 (1.1)	14 (1.8)
Any regorafenib containing regimen	84 (15.7)	41 (15.4)	125 (15.6)
No regorafenib-containing regimens	138 (25.8)	72 (27.1)	210 (26.3)

Source: Table 14.2.5.2.

[a] Includes 4 patients who had surgery plus other systemic anti-cancer therapy, and 2 patients who had surgery only.

Numbers analysed

In respect to efficacy results, of the 800 patients in the ITT Population, 798 received at least one dose of study medication as treated (AT) Population.

Table 33: Study Analysis Populations – RECOURSE study

	TAS-102 n (%)	Placebo n (%)	Total n (%)
Analysis Populations			
Intent-to-Treat (ITT) [All Randomised]	534	266	800
As-Treated (AT) Population	533	265	798
Tumour Response (TR) Population[a]	502 (94.0)	258 (97.0)	760 (95.0)
Randomised but not Treated[a]	1 (0.2)	1 (0.4)	2 (0.3)
Adverse event	1 (0.2)	0	1 (0.1)
Other (patient ineligible)	0	1 (0.4)	1 (0.1)

[a] Percentages based on the number of patients randomised (ITT).

Outcomes and estimation

Primary endpoint:

Overall survival

A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of 24 January 2014. For patients alive on the survival cut-off date, survival was censored on the cut-off date. Among patients with censored survival data, the median follow-up for OS was 8.29 months (range: 1.8 to 19.0 months).

Table 34: Primary analysis for overall Survival (ITT population) – RECOURSE study

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
Source: Table 14.2.1.1.

Table 35: Updated overall Survival as of 08 October 2014 (ITT Population) – RECOURSE study

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 randomized in the Placebo group, initiated TAS-102 treatment (cross-over) after the study was unblinded in May 2014. For the ITT analysis above, these patients were still counted in the Placebo group
Source: Table 26; 27Aug2015.

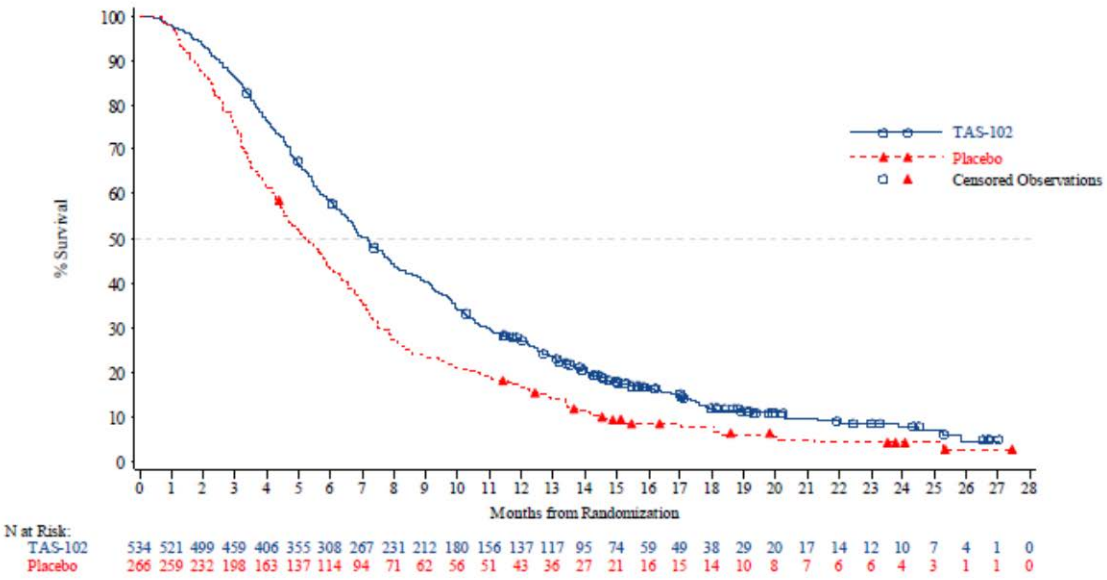


Figure 9: Survival status as of 08 October 2014 (ITT Population) - RECOURSE study

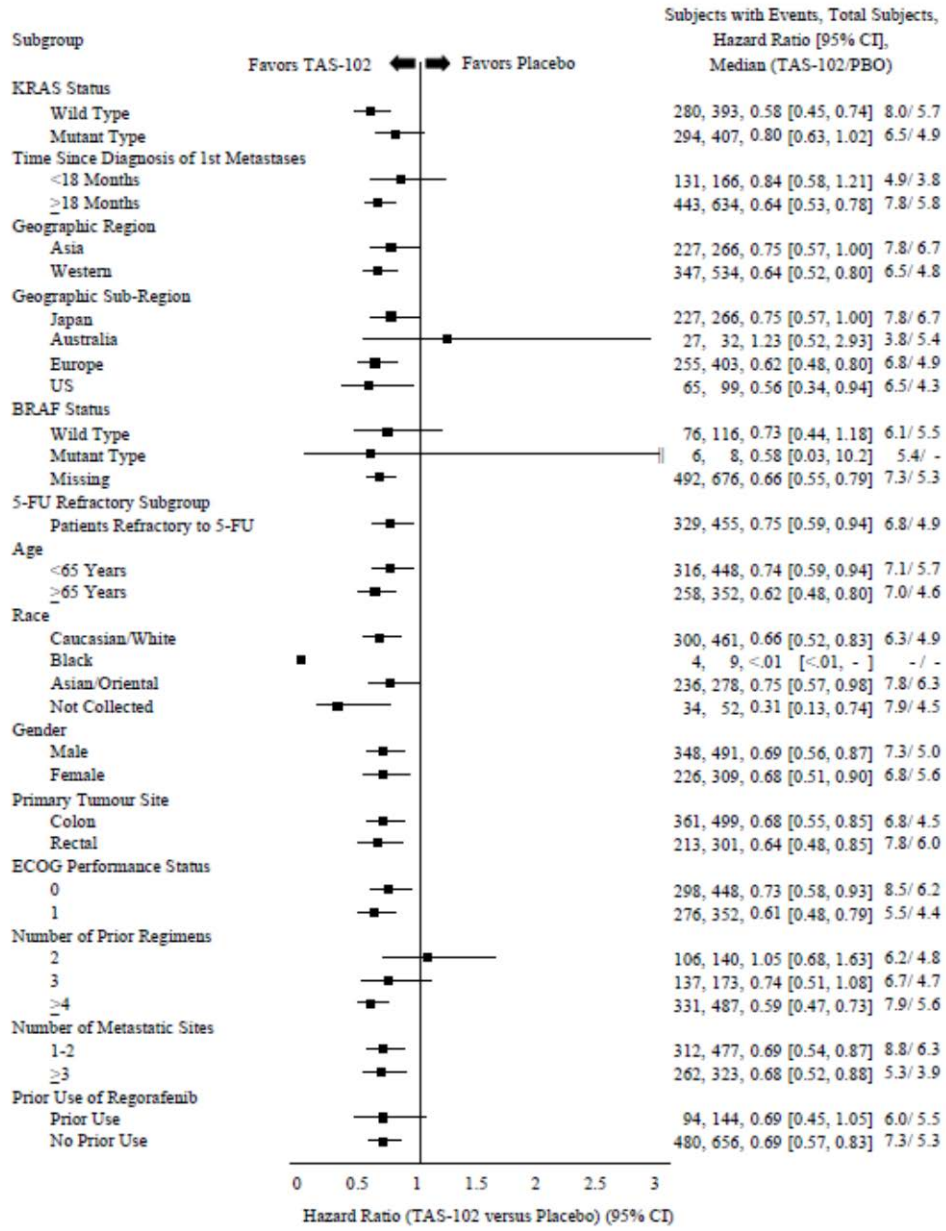


Figure 10: Forest Plot of Hazard Ratios for Treatment Effect on OS by Subgroups – RECOURSE study

The overall survival benefit was maintained after adjusting for all significant prognostic factors, namely, time since diagnosis of first metastasis, ECOG PS and number of metastatic sites (hazard ratio: 0.69; 95% CI [0.58 to 0.81]).

Secondary endpoints

Progression free survival

The PFS analysis was conducted at the pre-specified cut-off date of 31 January 2014 for non-survival data.

Table 36: Radiologic Progression-Free Survival (ITT Population) – RECOURSE study

Parameter	TAS-102 (N=534)		Placebo (N=266)	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (PFS event)	472 (88.4)		251 (94.4)	
Progressed	432 (80.9)		226 (85.0)	
Death	40 (7.5)		25 (9.4)	
Censored	62 (11.6)		15 (5.6)	
Discontinued follow-up	0 (0.0)		2 (0.8)	
Initiated other anti-tumour therapy	14 (2.6)		6 (2.3)	
Missed visit (>91 days since last response)	14 (2.6)		5 (1.9)	
Follow-up ongoing at time of analysis	34 (6.4)		2 (0.8)	
Progression-free survival (months)[a] [95% CI][b]				
25th percentile	1.7	[1.7, 1.8]	1.5	[1.4, 1.6]
Median	2.0	[1.9, 2.1]	1.7	[1.7, 1.8]
75th percentile	4.0	[3.8, 5.4]	1.9	[1.9, 2.0]
Hazard ratio [95% CI]	0.48 [0.41, 0.57]			
P-value[c]	<0.0001 (1-sided and 2-sided)			
Percent (%) of patients progression-free[a] [95% CI][d]				
At 2 months	(47.3)	[42.9, 51.5]	(20.8)	[16.0, 26.0]
At 4 months	(25.0)	[21.3, 28.8]	(4.7)	[2.5, 7.9]
At 6 months	(15.1)	[12.1, 18.5]	(1.4)	[0.4, 3.7]
At 8 months	(8.0)	[5.7, 10.8]	(1.4)	[0.4, 3.7]

[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

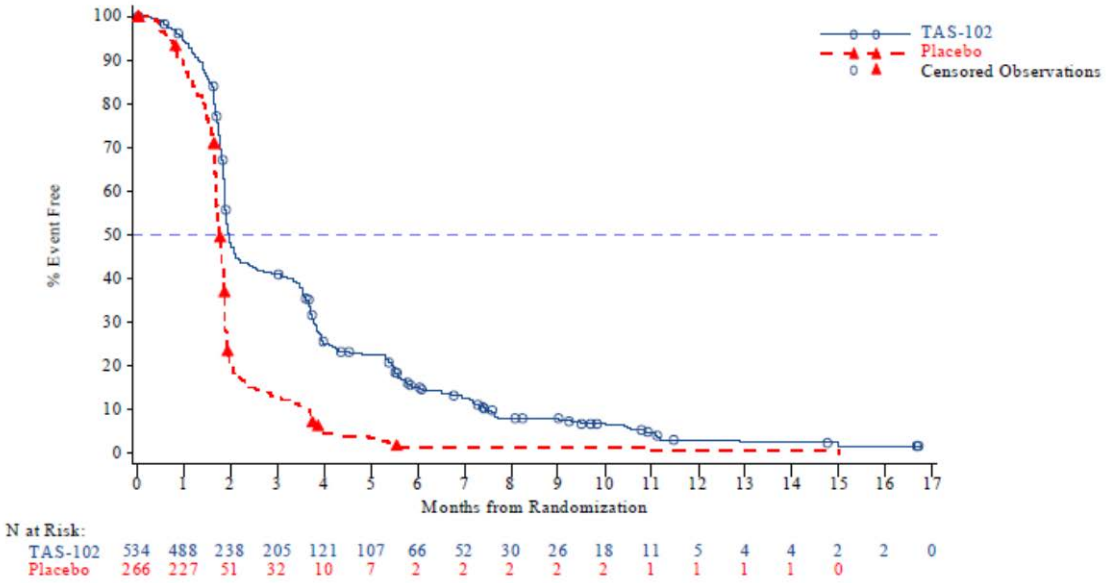


Figure 11: Radiologic Progression-Free Survival (ITT Population) – RECOURSE study

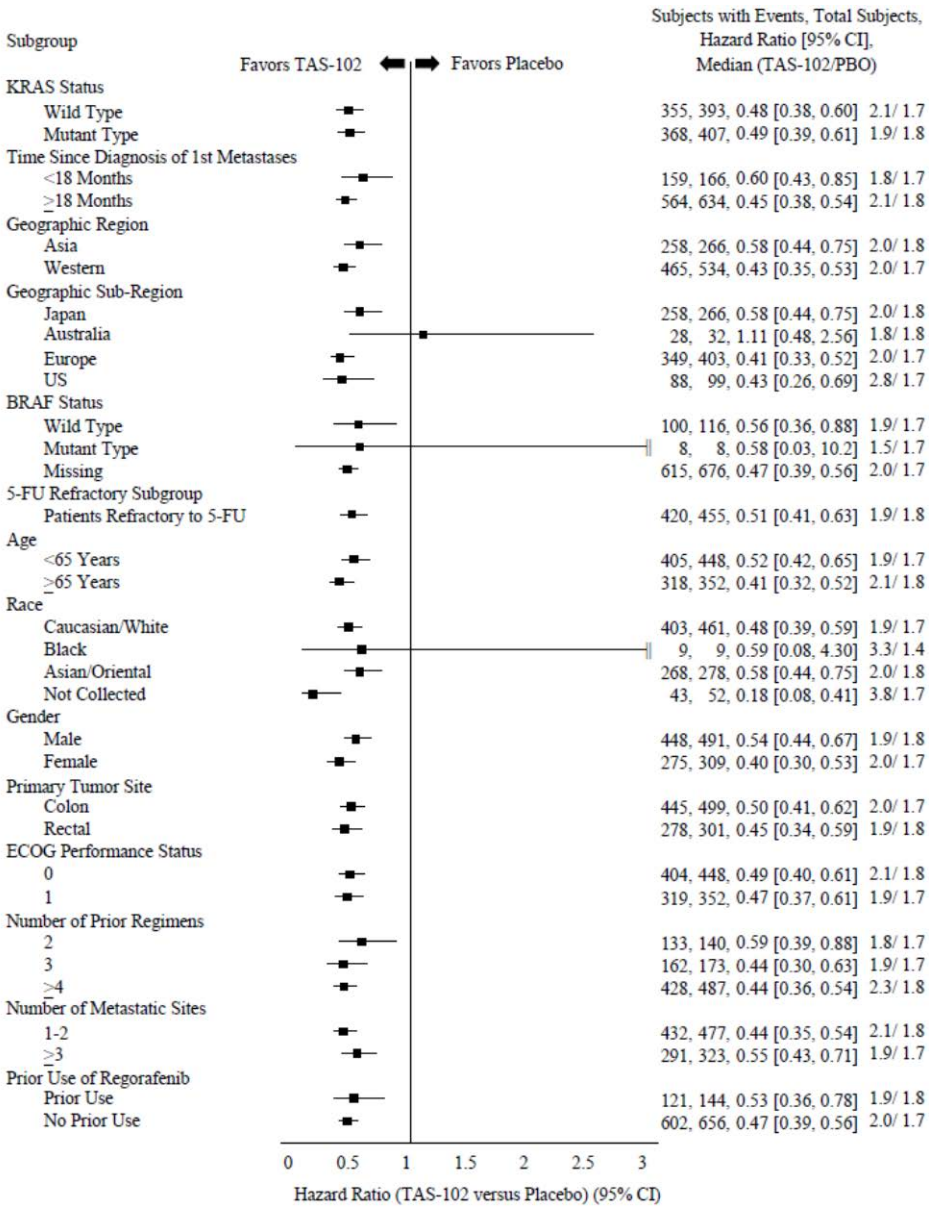


Figure 12: Forest Plot of Hazard Ratios for Treatment Effect on PFS by Subgroups – RECOURSE study

Time to treatment failure (TTF)

Median TTF was 1.9 months for the TAS-102 group versus 1.7 months for the placebo group with a HR of 0.50 (95% CI: 0.42, 0.58), p<0.0001), consistent with PFS results, considering the small number of patients who discontinued treatment for reasons other than disease progression or death.

Overall Response Rate/Disease Control Rate

Table 37: Best Overall Response Rate / Disease Control Rate (TR Population) – RECOURSE study

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[c]]	1.2 [-0.1, 2.5]			
P-value[d]	0.2862			
Difference in DCR (TAS-102 – placebo) [95% CI[c]]	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)

Duration of response and duration of stable disease

Only 8 patients in the TAS-102 group achieved tumour response. The median duration of response was 7.4 months (95% CI: 1.9 to 7.5 months).

Ancillary analyses

Time to ECOG Performance Status ≥2

An analysis of time to worsening ECOG PS status was pre-specified. The median time to ECOGPS ≥2 (ECOG PS 2 = ambulatory and capable of all self-care but unable to carry out any work activities) was 5.7 months for the TAS-102 group versus 4.0 months for the placebo group with HR of 0.66 (95% CI: 0.56, 0.78), p<0.0001 (stratified log-rank test).

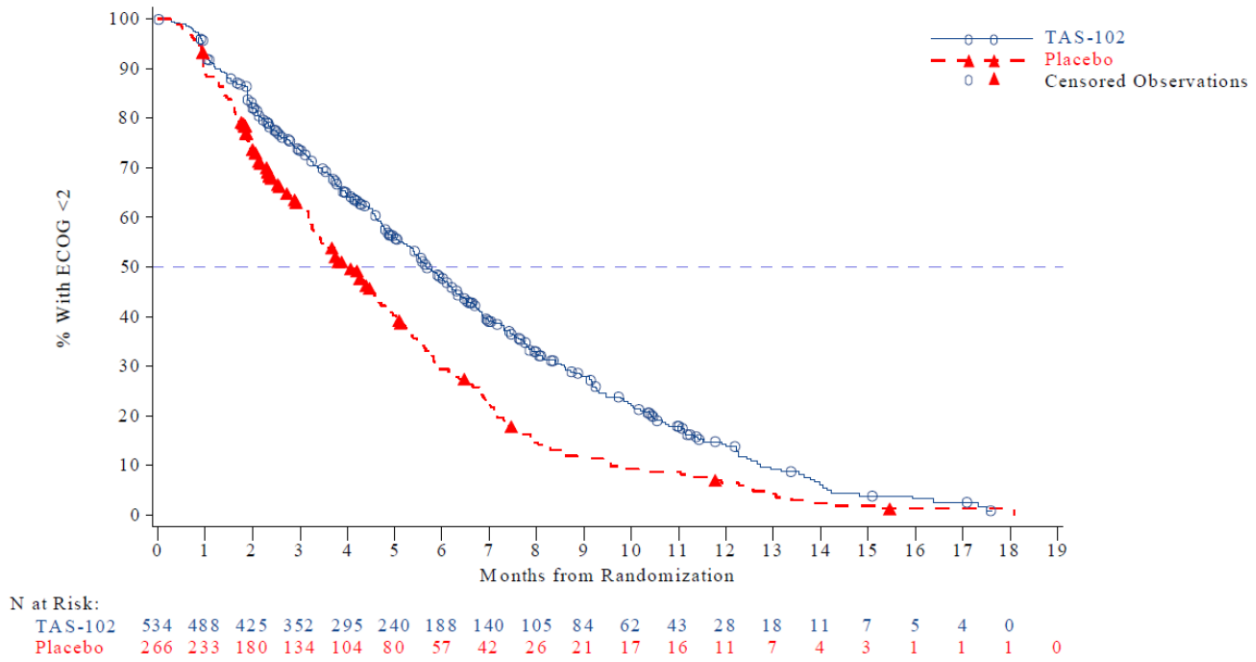


Figure 13: Time to ECOG Performance Status of ≥2 (ITT Population) – RECOURSE study

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of Efficacy for RECOURSE study

Title: RECOURSE			
Study identifier	TPU-TAS-102-301		
Design	Randomised, double blind, placebo-controlled		
Hypothesis	Superiority		
Treatments groups	Experimental		TAS-102: 35 mg/m^2/dose administered BID for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks. N= 534
	Control		Placebo N= 266
Endpoints and definitions	Primary endpoint	Overall survival	time from randomisation to death
	Secondary endpoint	Progression free survival	time from randomisation until investigator-assessed radiological disease progression or death
		TTF	time from randomisation until radiologic disease progression, permanent discontinuation of study treatment, or death
		ORR	proportion of patients with objective evidence of complete response (CR) or partial response (PR)
		DCR	proportion of patients with a best overall response of CR, PR, or SD

	Additional pre-specified analysis	Time to ECOG Performance Status ≥2	time from randomisation until patients has ECOG Performance Status ≥2

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat ITT population as of 8 October 2014 for OS only otherwise, data cut-off 24 January 2014		
Primary endpoint	Treatment group	TAS-102	Placebo
	Number of subject	534	266
	Median OS	7.2 months	5.2 months
	HR (95% CI) P value	HR 0.69 (0.59, 0.81) p<00001	
	1-year survival (%)	27.1	16.6
Secondary endpoints	Median PFS	2.0 months	1.7 months
	HR (95% CI) P value	HR 0.48 (0.41, 0.57) p<0.0001	
	TTF	1.9 months	1.7 months
	HR (95% CI) P value	HR 0.50 (0.42, 0.58) p<0.0001	
	ORR	1.6%	0.4%
	P value	P=0.2862	
	DCR	44.0%	16.3%
	P value	P<0.0001	
	Time to ECOG Performance Status ≥2	5.7 months	4.0 months
	HR (95% CI) P value	HR 0.66 (0.56, 0.78) P<0.0001	

Clinical studies in special populations

TAS-102 has not been studied in children (< 18 years) or in pregnant or lactating women. TAS 102 has been given to patients ≥75 years of age, but experience is limited.

Table 39: Summary table of older subjects included in the clinical development of TAS-102

	Age 65-74 (Older Subjects /Total)	Age 75-84 (Older Subjects /Total)	Age 85+ (Older Subjects /Total)
Controlled Trials (N=968)	353 (36.5)	74 (7.6)	0
Non Controlled trials (N=115)	30 (26.1)	8 (7.0)	1 (0.9)

Source: Table 37.13; 26 Aug 2015.

The effect of TAS-102 on overall survival was similar in patients <65 years and ≥65 years of age. There were no patients 85 years or older in the RECOURSE study and the Japanese phase 2 study.

Table 40: Overall survival by age subgroup (ITT population) – Recourse study

Age	TAS-102 n=534		Placebo n=266		TAS vs 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 -74	198	7.2 (6.3, 8.1)	94	4.5 (3.9, 5.9)	0.58 (0.43, 0.77)
75 – 84	36	6.5 (4.8, 9.1)	24	6.6 (2.9, 7.5)	0.89 (0.45, 1.74)

Moreover the majority of patients enrolled in the studies performed with TAS 102 to date were Caucasian/Whites and Asians (57.3% and 34.5% respectively), with data essentially lacking in patients with other races (e.g., blacks, etc.).Despite the low number of patients OS and PFS HRs in African Americans are in line with HRs in the overall study population and PK data support the potential benefit in this particular population.

For patients with moderate renal impairment, efficacy seems to be less compared to patients with normal to mild renal impairment. However, the small sample size for patients with moderate renal impairment might affect this result.

Table 41: Overall Survival by Renal Function Subgroup (ITT Population) – Recourse study

Renal Impairment	TAS-102		Placebo		TAS vs PBO
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
Normal	307	7.4 (6.6, 8,4)	145	5.3 (4.5, 5.9)	0.64 (0.51, 0.81)
Mild	178	6.7 (6.1, 8.0)	91	4.7 (3.9, 6.4)	0.71 (0.53, 0.96)
Moderate	47	6.9 (5.6, 10.7)	27	6.9 (4.4, 7.6)	0.85 (0.47, 1.56)

In RECOURSE, there were 303 patients with mild hepatic impairment (203 patients treated with TAS-102 and 100 patients on placebo) and an additional 5 patients who had moderate impairment (1 patient treated with TAS-102 and 4 patients on placebo). In patients with mild hepatic impairment, benefit was also demonstrated.

Table 42: Overall Survival by Hepatic Dysfunction subgroup (ITT Population) – Recourse study

Hepatic Dysfunction	TAS-102		Placebo		TAS vs PBO
	N	Median (95% CI)	N	Median (95% CI)	HR (95% CI)
Normal	325	9.9 (8.6, 11.1)	157	6.9 (5.9, 7.5)	0.63 (0.50, 0.80)
Mild G1	169	5.2 (4.6, 5.6)	83	3.5 (2.9, 4.0)	0.71 (0.53, 0.95)
Mild G2	34	5.2 (3.7, 7.8)	17	2.4 (1.2, 4.2)	0.44 (0.21, 0.92)

Supportive study

Study J003-10040030 was a randomised, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of TAS-102 versus placebo in Japanese patients with mCRC who had received prior two or more chemotherapeutic regimens including fluoropyrimidine, irinotecan, and oxaliplatin. One hundred and seventy-two (172) Japanese patients were randomised (2:1) to receive TAS-102 (35 mg/m^2/dose BID) given orally twice daily for 5 days a week with 2 days rest for 2 weeks, repeated every 4 weeks; or placebo. Patients were stratified by baseline ECOG performance status (PS=0, PS=1 or 2). The primary endpoint was overall survival. Of the 172 patients randomised, 2 patients discontinued prior to treatment and 1 treated patient was not eligible; All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; 82% of patients had received ≥3 prior chemotherapy regimens. Demographic and other baseline characteristics The patients were generally comparable.

Median OS (9.0 months) was higher in the TAS-102 group compared to the placebo group (6.6 months ; HR=0.56; 95% CI: [0.39, 0.81]; p = 0.0011). Median PFS assessed by independent review committee 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]; p < 0.0001).Overall response rate was 0.9% (1/112) in the TAS-102 group and 0.0% (0/57) in the placebo group. Disease control rate was 43.8% (49/112) in the TAS-102 group and 10.5% (6/57) in the placebo group (p<0.0001). The expression of TK1 and TPase proteins were not related to efficacy endpoints (DCR, PFS and OS) in either group.

2.5.3. Discussion on clinical efficacy

The clinical dose and dosing interval of TAS-102 has been supported by non-clinical studies but final dose and dosing interval i.e. 35 mg/m2 bid for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks, has been selected based on tolerability in patients with solid tumours and CRC.

Design and conduct of clinical studies

The evidence of efficacy of TAS-102 in patients with mCRC is based on the results of one pivotal study (RECOURSE), supported by the data of phase III study J003-1004030, enrolling Japanese patients with mCRC.

RECOURSE is a pivotal, phase III, multicentre, multinational, randomized, double blind, placebo-controlled study. The two arms design of the study with placebo plus BSC as comparator is considered acceptable, as patients enrolled in the trial had received all the standard treatment options currently available in EU except for the multikinase inhibitor regorafenib, which has not been granted MA at the time of the beginning of the study. However, with the enrolment of patients, 18% of patients in the RECOURSE study actually received regorafenib as prior therapy.

Half of patients in both groups had KRAS mutant and these were balanced between the two groups.

Although in the minority of patients, BRAF data were available and collected (15.5%). BRAF mutations were

found in 8 of the 124 subjects (6.5%), which is in line with the reported range in the literature. It is not likely that missing data on BRAF status would have led to a serious mismatch of assignment for this prognostic factor.

The selection of OS as primary endpoint of the pivotal RECOURSE study corresponds to the accepted standards of clinical cancer research and is in accordance with EMA guidelines (CPMP/EWP.205/95/Rev.3; CHMP/EWP/2330/99). Additionally, it needs to be noted that regorafenib became available after the pivotal study was already on-going, with enrolment almost completed.

Efficacy data and additional analyses

The study population in RECOURSE was similar to the general patient population with mCRC in several aspects. The treatment groups were comparable with respect to demographic and baseline characteristics.

The majority of patients (60.9%) had received ≥4 prior systemic cancer therapies, and over 45% of patients in each group had also received ≥4 lines in the metastatic setting, indicating that this was a heavily pretreated population. Of note, approximately 44% of the patients in both treatment groups were over the age of 65. Since elderly patients represent a large portion of the target population, this is considered acceptable.

The study did not included ECOG PS 2 patients which can be considered a limitation, due to the advanced disease setting, and that patients with ECOG PS 2 might represent a considerable proportion of the potential target population.

There was a significant improvement in overall survival of 2.0 months (median 7.2 months) for Lonsurf compared to the placebo (median OS 5.2 months; HR 0.69, p<0.0001). The percentage of patients surviving at 1 year was 27% in the Lonsurf group and 17% in the placebo group. The observed OS benefit is considered clinically relevant. The effect on OS was observed in several subgroups of the population (including race, geographic region, age, sex, ECOG PS, KRAS status, time since diagnosis of first metastasis, number of metastatic sites, and primary tumour site), with the exception of patients from Australia. The small sample size could potentially explain the lack of effect in this subgroup. No imbalance in post-study therapies between the two study arms was observed from the data provided. No OS benefit was observed in the subgroup of patients who received two or less prior therapies, and since PFS is consistent between subgroups with different lines of treatment, the lack of OS benefit in this subgroup is therefore considered to be caused by post-study treatments.

Among patients who received fluoropyrimidines at their last treatment and were resistant to this last regimen, treatment with Lonsurf was still efficacious (HR=0.75, 95% CI [0.59 to 0.94]). In addition, patients who received prior treatment with regorafenib (18%) benefit of TAS 102 was similar to patients who were not treated with this drug (HR=0.69).

In order to put the observed results into perspective, it is worth mentioning the results from the phase III study that led to the approval of regorafenib (Lancet.2013 Jan 26;381(9863):303-12), the only other agent currently marketed in the intended indication. Median OS was 6.4 months (IQR 3.6-11.8) in the regorafenib group and 5.0 months (IQR 2.8-10.4) in the placebo group (HR 0.77 for regorafenib vs. placebo, 95%CI 0.64-0.94; p=0.0052). Median PFS was 1.9 months (IQR 1.6-3.9) and 1.7 months (IQR 1.4-1.9) for regorafenib and placebo, respectively. ORR were low for both groups (1.0% and 0.4%, respectively, p=0.19) with no CR and a total of 6 PR (5 in regorafenib-treated patients and 1 in placebo). Aside from race and prior cancer therapy, both populations are very similar in terms of baseline demographic and disease characteristics. The main differences reside in the proportion of Asian patients included in the Lonsurf studies (approximately 34%, vs. 14% in the regorafenib study), minimum number of prior therapies (patients in TAS-102 study had received at least two prior regimens, vs. at least 1 prior regimen in the regorafenib study) and the proportion of patients with

available KRAS/BRAF status.

The OS results of TAS-102 appear to be supported by the investigator-assessed PFS data. A statistically significant increase in PFS was observed with TAS-102 compared with placebo (HR 0.48 [0.41, 0.57], p< 0.0001). Median PFS was 2.0 months (95% CI 1.9-2.1) in the TAS-102 arm and 1.7 months (95% CI 1.7-1.8) in the placebo arm. Results of supportive analyses of PFS including clinical progression and initiation of anti-tumour therapy as PFS events were consistent with that of the primary analysis of PFS. PFS benefit was maintained across all specified subgroups (KRAS status, time since diagnosis of first metastasis and geographical region).

The median time to ECOG PS ≥2 (ECOG PS 2 = ambulatory and capable of all self-care but unable to carry out any work activities) was longer for the Lonsurf group (5.7 months) than for the placebo group (4.0 months, HR of 0.66 (95% CI: 0.56, 0.78), p<0.0001). Unfortunately quality of life data was not planned when the study was designed as at that time, QoL instruments were not considered sensitive enough in such an advanced CRC patient population. Assessment of ECOG performance status might be subject of inter-physician differences.

Other patient reported outcomes able to indirectly assess clinical benefit for patients (e.g. use of analgesics, pain control, other specific disease related symptoms) have not been evaluated.

The supportive study J003-10040030 was a randomised, double-blind, placebo-controlled, multi-center study entirely conducted in Japan. A total of 172 patients who had received at least two or more chemotherapeutic regimens, including fluoropyrimidine, irinotecan, and oxaliplatin, were randomised. Study design, baseline population and disease characteristics (other than race and inclusion of ECOG PS 2 patients) were comparable with those of the pivotal study. In the supportive study, patients with ECOG PS =2 were allowed to enrol; however, the total number (n=4, 3 in TAS-102, 1 in placebo) is too limited to reach any conclusions.

In terms of efficacy results, the majority of the key results were mainly consistent with those obtained in RECOURSE. TAS-102 improved OS compared with placebo (median OS 9.0 and 6.6 months in the TAS-102 and placebo groups, respectively (HR=0.56; 95% CI: [0.39, 0.81]; p =0.0011).

From the data presented to date a subgroup benefiting most could not be identified. Unfortunately, no biomarker analysis has been provided by the applicant.

Based on the mechanism of action of FTD, the relationship between efficacy endpoints (PFS, and OS) and the expressions of thymidine kinase 1 (TK1, FTD activating enzyme) or thymidine phospholyrase (TP, FTD metabolizing enzyme) in tumours were investigated in an exploratory manner in Study J003-10040030. Using median cut-off data for tumour TK1 and TP, the correlation between Lonsurf clinical effects and the expression of TK1 or TP proteins was not observed.

Currently, there does not appear to be a predictive marker in the metastatic CRC setting to clearly define subpopulations that would derive greater or no benefit from TAS-102. The applicant is recommended to submit the results of a biomarker study in Japanese patients evaluating the TK1 protein expression and the following genes ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL and MSI status.

The effect of TAS 102 on overall survival was similar in patients <65 years and ≥65 years of age. There were no patients 85 years or older in the RECOURSE study and the Japanese phase 2 study.

No formal hepatic or renal impairment studies have been performed with TAS-102. The results of two PK studies investigating the PK of TAS-102 components/metabolites in patients with renal impairment (TO-TAS-102-107) and hepatic impairment (TO-TAS-102-106) will be submitted by December 2017 (see RMP).

For patients with moderate renal impairment, efficacy seems to be less compared to patients with normal to mild renal impairment. However, the small sample size for patients with moderate renal impairment might affect this result. In patients with mild and moderate hepatic impairment, benefit was also demonstrated.

2.5.4. Conclusions on the clinical efficacy

The 2.0 months gain in median OS associated to treatment with TAS-102 appears to be of clinical relevance considering the lack of subsequent therapies. A minority (18%) of patients received regorafenib as a prior treatment, which has not been granted MA at the beginning of the trial. However, the benefit in OS in patients who received this drug was comparable to those who did not receive regorafenib. Patients who received only 2 regimens did not benefit from TAS-102, which is considered to be due to the effect of post-study treatments, which are common available in these patients. No specific biomarker predictive for response to TAS-102 has been identified in RECOURSE. Additional analysis will be conducted post-approval as part of the exploratory genomic study.

2.6. Clinical safety

The safety database of TAS 102 consisted of data from 8 clinical studies including 6 open label studies and 2 randomized studies (safety database group 2), in which a total of 761 mCRC patients (safety data group 1) were exposed to TAS 102 in the proposed dose of 35 mg/m^2 bid.

Table 43: Overview of Clinical Studies Included in Integrated Safety Database - Patients with mCRC Receiving Starting Dose of 35 mg/m^2 BID

		Number of Treated Patients	
Study Design	**Study Number**	**TAS-102**	**Placebo**
Randomised, placebo-controlled, double-blind	TPU-TAS-102-301 (Phase 3, Global[a])	533	265
	J003-10040030 (Phase 2, Japan)	113	57
	Total for Safety Data Group 2	**646**	**322**
Open-label	J001-10040010 (Phase 1, Japan)	5	---
	J004-10040040 (Phase 1, Japan)	5	---
	TPU-TAS-102-101 (Phase 1, USA)	24	---
	TPU-TAS-102-102 (Phase 1, USA)	29	---
	TPU-TAS-102-103 (Phase 1, UK/USA)	33	---
	TPU-TAS-102-104 (Phase 1, USA)	19	---
	Total for Safety Data Group 1	**761**	---

[a] EU, Japan, USA and Australia

Moreover, deaths and SAEs as observed in other studies performed with TAS-102 administered in with other dose schedules or in other indications than mCRC were reported.

However, the safety analysis is focused on the data available from the phase 3 pivotal RECOURSE study, in which TAS-102 was compared with placebo in the target population.

Patient exposure

In the RECOURSE study 798 patients received at least one dose of study medication (533, Lonsurf; 265, placebo). In patients receiving Lonsurf the average duration of treatment was higher than for patients receiving placebo (12.65 and 6.76 weeks, respectively). Patients who were treated with Lonsurf had a mean relative dose intensity per cycle of 0.886 compared to 0.944 in the placebo group.

At the time of clinical cut-off for reporting of non-survival data (31-January 2014), 759 (95.1%) patients in the AT Population had discontinued study treatment and 39 patients (37, Lonsurf; 2, placebo) were continuing on treatment. The observed small differences in primary reasons for discontinuation of study treatment between the two treatment groups are not considered significant.

Table 44: Primary Reasons for Discontinuation from Study Treatment (AT Population)

	Number (%) of Patients					
	TAS-102 (N=533)		Placebo (N=265)		Total (N=798)	
Discontinued study treatment	496	(93.1)	263	(99.2)	759	(95.1)
Radiologic Progression	416	(78.0)	222	(83.8)	638	(79.9)
Clinical Disease Progression	33	(6.2)	31	(11.7)	64	(8.0)
Adverse Event/SAE	19	(3.6)	4	(1.5)	23	(2.9)
Death[a]	7	(1.3)	4	(1.5)	11	(1.4)
Withdrawal of Consent	12	(2.3)	1	(0.4)	13	(1.6)
Other	9[b]	(1.7)	1[c]	(0.4)	10	(1.3)
Continuing on study treatment as of 31Jan2014	37	(6.9)	2	(0.8)	39	(4.9)

a NOTE: Death was not a pre-specified reason for discontinuation on the eCRF. Patients with reason for discontinuation indicated as "Other" with verbatim of "death" or "died" in the description field are counted here.
b Patient 1: PI decision – "Progression due to decision of radiologist and Investigator"
Patient 2: Need for radiotherapy
Patient 3: Patient withdrew consent – "Patient decision not to continue on trial treatment"
Patient 4: PI decision – "Investigator decision to stop the treatment because of the hepatic progression"
Patient 5: Need for radiotherapy
Patient 6: PI decision – "Per physician discretion, overall tumor burden was increasing. It was not RECIST specific, but clinically significant"
Patient 7: CT scan report unavailable – "As suggested by the Sponsor we have changed the reason for stopping the treatment to Other because we do not have the Tc scan report; rdp was referred by phone"
Patient 8: Lack of compliance
Patient 9: PI decision
c Patient 10: Radiologic progression

In safety data group 2, more patients discontinued treatment in the placebo group (99.4%) than in the Lonsurf group (93.7%). The most common reason for treatment discontinuation was progression of disease, which was reported in 96% of patients in the placebo group compared to 84.8% of patient in the Lonsurf group. As of the database cut-off, more patients in the Lonsurf group (6.3%) compared to placebo group (0.6%) continued treatment. The average number of weeks of exposure per patient in Safety Data Group 2 was 12.9 weeks in the Lonsurf group and 6.4 weeks in the placebo group, and the median was 6.7 weeks and 5.7 weeks, respectively. Treatment discontinuation due to death was equally distributed between the two groups. More patients in the Lonsurf group (3.4%) discontinued treatment due to an AE/SAE than in the placebo group (1.6%), but the overall incidence was low.

Adverse events

Overall the type of AEs reported among Lonsurf - treated patients as observed across both safety data-groups was consistent.

The overview of adverse events from the RECOURSE study are presented in the below table.

Table 45: Overview of Adverse Events – Recourse study (AT Population)

Number (%) of patients with:	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)
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 with outcome of death	17 (3.2)	30 (11.3)
Any AE resulting in discontinuation	55 (10.3)	36 (13.6)

[a] Per protocol, death due to disease progression was not reported as an SAE.
Source: CSR TPU-TAS-102-301, Table 35

The most frequently reported AEs in patients treated with Lonsurf were nausea, anaemia, decreased appetite, fatigue, diarrhoea, neutropenia, neutrophil count decreased, vomiting, and white blood cell (WBC) count decreased as an AE.

The most frequently reported ≥Grade 3 treatment-related AEs were neutropenia, neutrophil count decreased, anaemia and WBC count decreased.

Table 46: Summary of adverse events occurring in ≥5% of patients in either treatment group summarised by MedDRA SOC and preferred term– Recourse study (AT Population)

MedDRA System Organ Class (SOC)	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any adverse event	**524 (98.3)**	**370 (69.4)**	**247 (93.2)**	**137 (51.7)**
Blood and lymphatic system disorders				
Anaemia	214 (40.2)	86 (16.1)	22 (8.3)	7 (2.6)
Leukopenia	29 (5.4)	13 (2.4)	0 (0.0)	0 (0.0)
Neutropenia	156 (29.3)	107 (20.1)	0 (0.0)	0 (0.0)
Thrombocytopenia	37 (6.9)	11 (2.1)	1 (0.4)	1 (0.4)
Gastrointestinal disorders				
Abdominal pain	79 (14.8)	11 (2.1)	36 (13.6)	10 (3.8)
Abdominal pain upper	38 (7.1)	1 (0.2)	12 (4.5)	1 (0.4)
Constipation	81 (15.2)	1 (0.2)	40 (15.1)	3 (1.1)
Diarrhoea	170 (31.9)	16 (3.0)	33 (12.5)	1 (0.4)
Nausea	258 (48.4)	10 (1.9)	63 (23.8)	3 (1.1)
Stomatitis	42 (7.9)	2 (0.4)	16 (6.0)	0 (0.0)
Vomiting	148 (27.8)	11 (2.1)	38 (14.3)	1 (0.4)
General disorders and administration site conditions				
Asthenia	97 (18.2)	18 (3.4)	30 (11.3)	8 (3.0)
Fatigue	188 (35.3)	21 (3.9)	62 (23.4)	15 (5.7)
General physical deterioration	21 (3.9)	18 (3.4)	15 (5.7)	12 (4.5)
Mucosal inflammation	30 (5.6)	2 (0.4)	12 (4.5)	0 (0.0)
Oedema peripheral	53 (9.9)	1 (0.2)	27 (10.2)	2 (0.8)
Pyrexia	98 (18.4)	6 (1.1)	37 (14.0)	1 (0.4)
Investigations				
Alanine aminotransferase increased	25 (4.7)	3 (0.6)	15 (5.7)	3 (1.1)
Aspartate aminotransferase increased	30 (5.6)	7 (1.3)	22 (8.3)	7 (2.6)
Blood alkaline phosphatase increased	47 (8.8)	18 (3.4)	26 (9.8)	13 (4.9)
Blood bilirubin increased	45 (8.4)	21 (3.9)	20 (7.5)	10 (3.8)
Neutrophil count decreased	148 (27.8)	85 (15.9)	1 (0.4)	0 (0.0)
Platelet count decreased	81 (15.2)	13 (2.4)	6 (2.3)	0 (0.0)
Weight decreased	41 (7.7)	1 (0.2)	27 (10.2)	0 (0.0)
White blood cell count decreased	146 (27.4)	55 (10.3)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders				
Decreased appetite	208 (39.0)	19 (3.6)	78 (29.4)	13 (4.9)
Hyponatraemia	16 (3.0)	7 (1.3)	14 (5.3)	4 (1.5)
Musculoskeletal and connective tissue disorders				
Back pain	42 (7.9)	9 (1.7)	18 (6.8)	2 (0.8)
Neoplasms, benign, malignant and unspecified				
Tumour pain	30 (5.6)	3 (0.6)	23 (8.7)	5 (1.9)
Nervous system disorders				
Dysgeusia	36 (6.8)	0 (0.0)	6 (2.3)	0 (0.0)
Headache	29 (5.4)	0 (0.0)	13 (4.9)	0 (0.0)
Psychiatric disorders				
Insomnia	24 (4.5)	0 (0.0)	25 (9.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Cough	57 (10.7)	2 (0.4)	30 (11.3)	2 (0.8)
Dyspnoea	56 (10.5)	14 (2.6)	34 (12.8)	10 (3.8)
Skin and subcutaneous tissue disorders				
Alopecia	36 (6.8)	0 (0.0)	3 (1.1)	0 (0.0)
Vascular disorders				
Hypertension	19 (3.6)	8 (1.5)	14 (5.3)	10 (3.8)

The treatment-related adverse events are summarised in the table below.

Table 47: Treatment-Related Adverse Events Reported in ≥5% of Subjects – RECOURSE study (AT Population)

MedDRA System Organ Class Preferred Term	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Any treatment-related adverse event	**457 (85.7)**	**261 (49.0)**	**145 (54.7)**	**26 (9.8)**
Blood and lymphatic system disorders				
Anaemia	168 (31.5)	65 (12.2)	12 (4.5)	5 (1.9)
Neutropenia	153 (28.7)	107 (20.1)	0 (0.0)	0 (0.0)
Thrombocytopenia	30 (5.6)	9 (1.7)	1 (0.4)	1 (0.4)
Gastrointestinal disorders				
Constipation	33 (6.2)	0 (0.0)	4 (1.5)	0 (0.0
Diarrhoea	126 (23.6)	12 (2.3)	24 (9.1)	0 (0.0)
Nausea	210 (39.4)	5 (0.9)	29 (10.9)	0 (0.0)
Stomatitis	38 (7.1)	2 (0.4)	8 (3.0)	0 (0.0)
Vomiting	107 (20.1)	3 (0.6)	12 (4.5)	0 (0.0)
General disorders and administration site conditions				
Asthenia	58 (10.9)	9 (1.7)	12 (4.5)	2 (0.8)
Fatigue	132 (24.8)	11 (2.1)	27 (10.2)	5 (1.9)
Investigations				
Neutrophil count decreased	145 (27.2)	83 (15.6)	1 (0.4)	0 (0.0)
Platelet count decreased	77 (14.4)	13 (2.4)	4 (1.5)	0 (0.0)
White blood cell count decreased	140 (26.3)	52 (9.8)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders				
Decreased appetite	141 (26.5)	9 (1.7)	30 (11.3)	0 (0.0)
Nervous system disorders				
Dysgeusia	27 (5.1)	0 (0.0)	3 (1.1)	0 (0.0)
Skin and subcutaneous tissue disorders				
Alopecia	31 (5.8)	0 (0.0)	3 (1.1)	0 (0.0)

Source: TPU-TAS-102-301, Table 14.3.1.2.

Liver impairment

Liver impairment-related AEs, such as jaundice and ascites were almost as frequently reported in the placebo group (32.3%, grade ≥3 15.8%) as in the TAS-102 group (31.8%, grade ≥3 13.2%) in safety database group 2. Liver impairment-related AEs leading to discontinuation of treatment were more common observed in the placebo group (5.0%) than in the TAS-102 group (1.4%). Fatal liver impairment occurred also more frequently in the placebo group (2.2%) than in the TAS-102 group (0.5%).

Renal impairment

Renal impairment-related AEs were more frequent in the Lonsurf group (9.0% of patients) compared to the placebo group (4.9% of patients). The renal impairment-related AEs with the greatest frequency difference between groups were proteinuria (Lonsurf, 22 [4.1%]; placebo, 5 [1.9%]); all of these AEs were of Grade 1 or 2 severity. Renal impairment led to treatment discontinuation in 0.4% of patients in both Lonsurf and placebo group.

Table 48: Sponsor-defined Renal Abnormality-related Adverse Events – Recourse study (AT Population)

Category	Number (%) of Patients			
	TAS-102 (N=533)		Placebo (N=265)	
Preferred Term	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)

Source: Tables 14.3.1.15, 14.3.1.16, and 14.3.1.17.

Infection related AEs

In the TAS-102 group, infection-related AEs (including leukopenia and neutropenia) were more frequent than in the placebo group (73.7% and 33.2%, respectively); however, only 6 (1.1%) patients in the TAS-102 group discontinued treatment due to infection related AEs). Three patients in the TAS-102 group experienced fatal infections (i.e. sepsis, liver abscess and pneumonia).

Table 49: Sponsor-defined Infection-related Adverse Events (AT Population)

Category	Number (%) of Patients			
	TAS-102 (N=533)		Placebo (N=265)	
Preferred Term	All Grades	≥Grade 3	All Grades	≥Grade 3
Any infection-related AE	393 (73.7)	241 (45.2)	88 (33.2)	37 (14.0)
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

Source: Tables 14.3.1.21, 14.3.1.22, and 14.3.1.23.

Treatment-related infections occurred more frequently in Lonsurf-treated patients (5.6%) compared to those receiving placebo (1.9%).

Bleeding events

Bleeding events occurred at similar rates in the TAS-102 (9.0%; grade ≥3 0.8%) and placebo group (8.7%) in safety database group 2.. However, the incidence of events ≥Grade 3 was lower in TAS-102 (0.8%) than on placebo group (3.1%).

Thromboembolic events

Thromboembolic events (TEEs) were more frequent in the TAS-102 group (3.7%) compared to the placebo group (1.9%) in safety database group 2.. Of these events, nine patients experienced a pulmonary embolism (PE), whereas no PEs were reported in the placebo group. All PEs were ≥Grade 3, including one fatal case. Seven out of the 9 cases were considered unrelated to study medication, including the fatal case.

Handfoot syndrome

In RECOURSE, hand-foot syndrome was equally distributed in 2.3% patients in the TAS-102 and 2.3% of patients in the placebo group and was of low grade (1-2).

Fatigue

In both study groups, (35.3% (3.9% grade 3-4) for patients receiving TAS-102 and 23.4% (5.7% grade3-4) of patients receiving placebo, fatigue was commonly reported and in the majority of cases was considered related to treatment. Asthenia was reported in 18.2% (grade 3 and 4 3.4%) of patients in the TAS-102 group and 11.3% (grade 3 and 4: 3.0%) of patients in the placebo group.

QT prolongation

In Study TPU-TAS-102-103, cardiac safety and QT prolongation correlated to PK of Lonsurf was investigated in 30 patients following a single dose and following multiple doses (BID on Days 1through 5, followed by a recovery period from Day 6 through Day 7 and BID dosing on Days 8 through 12). No patient had a QT, QTcF, or QTcB interval >500 msec at any time point; TAS-102 did not appear to be arrhythmogenic.

Other Cardiac events

In RECOURSE study, the overall incidence of cardiac AEs was low in both treatment groups (Lonsurf, 3.9%; placebo, 4.5%). In order to further examine the incidence of events related to arrhythmia versus those related to cardiac ischaemia, AE preferred terms categorized as either arrhythmic or ischaemic events (Sponsor-identified) were summarized. The overall incidence of arrhythmic events was 2.8% in the TAS-102 group and 3.4% in the placebo group, while the incidence of cardiac ischaemic events was 0.6% and 0.4%, respectively.

Adverse events of special interest (AESI)

Consistent with the pharmacology of TAS-102, the pre-clinical toxicology profile and the mechanism of action of TAS-102 and the population treated, AEs of special interest (AESI) included myelosuppression, and gastro-intestinal disorders.

Myelosuppression

In the pivotal RECOURSE trial, the frequency of haematologic impairment-related AEs, primarily neutropenia, anaemia and other events associated with myelosuppression, was much higher in the TAS-102 group (70.9%) than in the placebo group (15.5%).

In 0.3% of patients in the TAS-102 group, the occurrence of anaemia led to treatment discontinuation in the TAS-102 group. Blood transfusion was administered to 16.9% of patients.

Treatment related neutropenia events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of granulocyte colony-stimulating factor (G-CSF; 9.4% of patients receiving TAS-102. The incidences of febrile neutropenia leading to hospitalisation in the TAS-102 and placebo groups were 2.6% and 0.0%, respectively. In 0.2% neutropenia led to treatment discontinuation of TAS-102. Three (0.5%) patients died of fatal infections related to TAS-102.

Gastro-intestinal disorders

In the RECOURSE study, treatment related GI disorders occurred more frequently in the TAS-102 arm compared to the placebo arm. Stomatitis was reported in 7.9% of patients receiving TAS-102 compared to 6.0% of those receiving placebo, with a very low rate of Grade 3/4 stomatitis (0.4%) in the TAS-102 group, which was manageable. Mucosal inflammation was reported for 5.6% of patients in the TAS-102 group and 4.5% of patients in the placebo group.

Dose reduction and dose delays

In the TAS-102 group of Safety Data Group 2, a total of 95 (14.7%) patients had dose reductions: 69 (10.7%) patients had a single dose reduction, 23 (3.6%) patients had 2 reductions, and 3 (0.5%) patients had ≥3 reductions. In the placebo group, 0.9% of patients had one dose reduction. The median number of cycles until the first dose reduction was 3.0 (range 2 to 13). In RECOURSE study, The most frequent AEs leading to dose reduction in the TAS-102 group were: neutropenia (17 [3.2%]), anaemia (11 [2.1%]), neutrophil count decreased (10 [1.9%]), febrile neutropenia (10 [1.9%),] fatigue (8 [1.5%]), and diarrhoea (7 [1.3%])

Dose delays occurred frequently in the TAS-102 group: More than half (56.0%) of patients experienced a delay of ≥4 days in initiation of at least 1 cycle, and 26.4% of patients who initiated ≥2 cycles) experienced a delay of ≥8 days in initiation of at least 1 cycle. Almost half of the total of TAS-102 cycles (49.1%) were delayed by at least 4 days and 13.8% were delayed by at least 8 days. 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) Delays in cycle initiation were primarily due to neutropenia/decreased neutrophil count and anaemia.

Adverse drug reactions as reflected in the product information

The following criteria were used to establish causal relationship of the AE with Lonsurf:

AEs were considered as related if it follows a reasonable temporal sequence from administration of study medication and, one of the following conditions is true: positive de-challenge or re-challenge or the event cannot be reasonably explained by the patient's clinical state and/or other administered therapies.

AEs were considered as not related when there is no reasonable possibility that the study medication caused the event. Reasonable possibility is illustrated by the following examples:

- a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;

- one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to drug

- an aggregate analysis of specific events in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The table below provides the list of ADRs and their respective frequencies.

Table 50: Adverse drug reactions reported with Lonsurf in the RECOURSE study

System Organ Class[a]	Very Common (# Patients (%) – Term)	Common (# Patients (%) – Term)	Uncommon (# Patients (%) – Term)
Blood and Lymphatic System Disorders	287 (53.8%) - Neutropenia 165 (31.0%) - Leukopenia 171 (32.1%) - Anaemia 106 (19.9%) - Thrombocytopenia	20 (3.8%) - Febrile Neutropenia 22 (4.1%) - Lymphopenia 7 (1.3%) - Monocytosis	1 (0.2%) - Pancytopenia 1 (0.2%) - Granulocytopenia 2 (0.4%) - Monocytopenia 3 (0.6%) - Erythropenia 1 (0.2%) - Leukocytosis
Cardiac Disorders			1 (0.2%) - Angina Pectoris 2 (0.4%) - Arrhytmia 3 (0.6%) - Palpitations
Ear and Labyrinth Disorders			2 (0.4%) - Vertigo 1 (0.2%) - Ear Discomfort
Eye Disorders			1 (0.2%) - Visual Acuity Reduced 1 (0.2%) - Vision Blurred 1 (0.2%) - Diplopia 1 (0.2%) - Cataract 3 (0.6%) - Conjunctivitis 1 (0.2%) - Dry Eye
Gastrointestinal Disorders	126 (23.6%) - Diarrhoea 210 (39.4%) - Nausea 107 (20.1%) - Vomiting	29 (5.4%) - Abdominal Pain 33 (6.2%) - Constipation 38 (7.1%) - Stomatitis 8 (1.5%) - Oral Disorder	1 (0.2%) - Enterocolitis Haemorrhagic 2 (0.4%) - Gastrointestinal Haemorrhage 1 (0.2%) - Pancreatitis Acute 1 (0.2%) - Ascites 1 (0.2%) - Ileus 1 (0.2%) - Subileus 1 (0.2%) - Colitis 2 (0.4%) - Gastritis 1 (0.2%) - Reflux Gastritis 1 (0.2%) - Oesophagitis 2 (0.4%) - Impaired Gastric Emptying 1 (0.2%) - Abdominal Distension 1 (0.2%) - Anal Inflammation 1 (0.2%) - Mouth Ulceration 4 (0.8%) - Dyspepsia 2 (0.4%) - Gastrooesophageal Reflux Disease 1 (0.2%) - Proctalgia 1 (0.2%) - Buccal Polyp 1 (0.2%) - Gingival Bleeding 2 (0.4%) - Glossitis 1 (0.2%) - Periodontal Disease 1 (0.2%) - Tooth Disorder 1 (0.2%) - Retching 2 (0.4%) - Flatulence 1 (0.2%) - Breath Odour
General Disorders and Administration Site Conditions	188 (35.3%) - Fatigue	26 (4.9%) - Pyrexia 12 (2.3%) - Oedema 26 (4.9%) - Mucosal Inflammation 19 (3.6%) - Malaise	1 (0.2%) - General Physical Health Deterioration 4 (0.8%) - Pain 4 (0.8%) - Feeling of Body Temperature Change 1 (0.2%) - Xerosis
Hepatobiliary Disorders		12 (2.3%) - Hyperbilirubinaemia	1 (0.2%) - Hepatotoxicity 1 (0.2%) - Biliary Dilatation
Infections and Infestation		8 (1.5%) - Lower Respiratory Tract Infection 6 (1.1%) - Upper Respiratory Tract Infection	1 (0.2%) - Septic Shock[c] 1 (0.2%) - Enteritis Infectious 1 (0.2%) - Lung Infection 4 (0.8%) - Biliary Tract Infection 2 (0.4%) - Influenza 5 (0.9%) - Urinary Tract Infection 1 (0.2%) - Gingival Infection

System Organ Class[a]	Very Common (# Patients (%) – Term)	Common (# Patients (%) – Term)	Uncommon (# Patients (%) – Term)
			2 (0.4%) - Herpes Zoster 1 (0.2%) - Tinea Pedis 1 (0.2%) - Candidiasis 1 (0.2%) - Bacterial Infection 2 (0.4%) – Infection
Investigations		17 (3.2%) - Hepatic Enzyme Increased 14 (2.6%) - Blood Alkaline Phosphatase Increased 14 (2.6%) - Weight Decreased	4 (0.8%) - Blood Creatinine Increased 1 (0.2%) - Electrocardiogram QT Prolonged 2 (0.4%) - International Normalised Ratio Increased 1 (0.2%) - Activated Partial Thromboplastin Time Prolonged 1 (0.2%) - Blood Urea Increased 4 (0.8%) - Blood Lactate Dehydrogenase Increased 1 (0.2%) - Protein Total Decreased 1 (0.2%) - C-Reactive Protein Increased 3 (0.6%) - Haematocrit Decreased
Metabolism and Nutrition Disorders	141 (26.5%) - Decreased Appetite	10 (1.9%) - Hypoalbuminaemia	2 (0.4%) - Dehydration 1 (0.2%) - Hyperglycaemia 2 (0.4%) - Hyperkalaemia 4 (0.8%) - Hypokalaemia 2 (0.4%) - Hypophosphataemia 1 (0.2%) - Hypernatraemia 5 (0.9%) - Hyponatraemia 1 (0.2%) - Hypocalcaemia 1 (0.2%) - Gout
Musculoskeletal and Connective Tissue Disorders			1 (0.2%) - Joint Swelling 1 (0.2%) - Arthralgia 1 (0.2%) - Bone Pain 2 (0.4%) - Myalgia 1 (0.2%) - Musculoskeletal Pain 1 (0.2%) - Muscular Weakness 2 (0.4%) - Muscle Spasms 2 (0.4%) - Pain in Extremity 1 (0.2%) - Sensation of Heaviness
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)			3 (0.6%) - Cancer Pain
Nervous System Disorders		27 (5.1%) - Dysgeusia 6 (1.1%) - Neuropathy Peripheral 6 (1.1%) - Dizziness 7 (1.3%) - Headache	2 (0.4%) - Neurotoxicity 1 (0.2%) - Dysaesthesia 1 (0.2%) - Hyperaesthesia 1 (0.2%) - Hypoaesthesia 1 (0.2%) - Syncope 5 (0.9%) - Paraesthesia 1 (0.2%) - Burning Sensation 1 (0.2%) - Lethargy
Psychiatric Disorders		6 (1.1%) - Insomnia	2 (0.4%) - Anxiety
Renal and Urinary Disorder		15 (2.8%) - Proteinuria	1 (0.2%) - Renal Failure 1 (0.2%) - Cystitis Noninfective 4 (0.8%) - Micturition Disorder 4 (0.8%) - Haematuria 1 (0.2%) - Leukocyturia
Reproductive System and Breast Disorders			1 (0.2%) - Menstrual Disorder
Respiratory, Thoracic and Mediastinal Disorders		10 (1.9%) - Dyspnoea 7 (1.3%) - Cough	2 (0.4%) - Pulmonary Embolism 1 (0.2%) - Pleural Effusion 1 (0.2%) - Rhinorrhoea 5 (0.9%) - Dysphonia 1 (0.2%) - Oropharyngeal Pain 4 (0.8%) - Epistaxis
Skin and Subcutaneous Tissue Disorders		9 (1.7%) - Palmar-Plantar Erythrodysaesthesia Syndrome[b] 16 (3.0%) - Rash 31 (5.8%) - Alopecia 13 (2.4%) - Pruritus 14 (2.6%) - Dry Skin	1 (0.2%) - Skin Exfoliation 1 (0.2%) - Urticaria 1 (0.2%) - Photosensitivity Reaction 1 (0.2%) - Erythema 3 (0.6%) - Acne 5 (0.9%) - Hyperhidrosis 1 (0.2%) - Blister 4 (0.8%) - Nail Disorder
Vascular Disorders		8 (1.5%) - Flushing	1 (0.2%) - Embolism 3 (0.6%) - Hypertension 3 (0.6%) - Hypotension

Serious adverse event / deaths / other significant events

Data from randomized trials (Safety Data Group 2) showed that SAEs were reported for 27.7% of patients in the Lonsurf group and 29.2% of patients in the placebo group, while treatment-related SAEs were reported for 9.8% of patients in the Lonsurf group and 0.6% of patients in the placebo group. Most common treatment related SAEs for TAS-102 were febrile neutropenia (2.8%) and anaemia (1.5%).

Gastrointestinal SAEs were reported for 7.1% of patients in the Lonsurf group and 8.4% of patients in the placebo group, but were considered treatment-related in only 2.2% of patients in the Lonsurf group and 0.3% of patients in the placebo group. The most frequent gastrointestinal SAEs in the Lonsurf group were abdominal pain (1.4%) and vomiting (1.1%). Serious infections were reported for 4.8% of patients in the Lonsurf group (2.3% treatment related) and 4.3% in the placebo group (0.3% treatment related).

Fatal adverse events from Safety Data Groups 1 and 2 are summarised in the table below. One fatal (Grade 5) AE in the TAS-102 group (septic shock) was considered related to study treatment in the Safety Data Group 2.

Additional fatal AEs reported in Safety Data 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.

Table 51: Fatal Adverse Events: Safety Data Groups 1 and 2

MedDRA SOC Preferred Term	Group 1 TAS-102 (N=761) n (%)		Group 2 TAS-102 (N=646) n (%)		Placebo (N=322) n (%)	
Any fatal adverse event	20	(2.6)	18	(2.8)	30	(9.3)
Cardiac disorders	0		0		1	(0.3)
Cardio-respiratory arrest	0		0		1	(0.3)
Gastrointestinal disorders	1	(0.1)	0		5	(1.6)
Abdominal pain	0		0		1	(0.3)
Gastrointestinal haemorrhage	0		0		1	(0.3)
Haematemesis	0		0		1	(0.3)
Haematochezia	1	(0.1)	0		0	
Intestinal perforation	0		0		1	(0.3)
Small intestinal obstruction	0		0		1	(0.3)
General disorders and administration site conditions	6	(0.8)	6	(0.9)	8	(2.5)
General physical health deterioration	6	(0.8)	6	(0.9)	8	(2.5)
Hepatobiliary disorders	2	(0.3)	2	(0.3)	8	(2.5)
Bile duct obstruction	0		0		1	(0.3)
Hepatic failure	2	(0.3)	2	(0.3)	6	(1.9)
Jaundice	0		0		1	(0.3)
Infections and infestations	4	(0.5)	3	(0.5)	0	
Liver abscess	1	(0.1)	1	(0.2)	0	
Pneumonia staphylococcal	1	(0.1)	1	(0.2)	0	
Sepsis	1	(0.1)	1	(0.2)	0	
Septic shock	2	(0.3)	1	(0.2)	0	
Staphylococcal infection	1	(0.1)	0		0	
Metabolism and nutrition disorders	0		0		1	(0.3)
Acidosis	0		0		1	(0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0		0		2	(0.6)
Lymphangiosis carcinomatosa	0		0		1	(0.3)
Malignant ascites	0		0		1	(0.3)
Nervous system disorders	0		0		3	(0.9)
Cognitive disorder	0		0		1	(0.3)
Haemorrhage intracranial	0		0		1	(0.3)
Hepatic encephalopathy	0		0		1	(0.3)
Renal and urinary disorders	2	(0.3)	2	(0.3)	2	(0.6)
Renal failure	0		0		1	(0.3)
Renal failure acute	2	(0.3)	2	(0.3)	0	
Renal impairment	0		0		1	(0.3)
Respiratory, thoracic and mediastinal disorders	5	(0.7)	5	(0.8)	7	(2.2)
Dyspnoea	1	(0.1)	1	(0.2)	4	(1.2)
Interstitial lung disease	1	(0.1)	1	(0.2)	0	
Pleural effusion	1	(0.1)	1	(0.2)	1	(0.3)
Pulmonary congestion	0		0		1	(0.3)
Pulmonary embolism	1	(0.1)	1	(0.2)	0	
Pulmonary oedema	1	(0.1)	1	(0.2)	0	
Respiratory arrest	0		0		1	(0.3)

Laboratory findings

In the pivotal RECOURSE trial 37.9% of patients in the TAS-102 group experienced Grade 3 or Grade 4 neutropenia and 113 (21.4%) patients experienced Grade 3 or 4 leukopenia during treatment, while no Grade 3 or 4 values were observed for these parameters in the placebo group. Grade 3 or 4 lymphocytopenia (18.2%), anaemia (18.2%) and thrombocytopenia (4.5%) were all more frequent in the TAS-102 group than in the placebo group. Median haemoglobin, neutrophil counts and thrombocytes gradually decreases with start but remained stable from cycle 4,1, and 3 respectively.

Table 52: Grade 3 or 4 Abnormalities in Haematology Parameters that Worsened from Baseline (AT Population) in RECOURSE

	Maximum CTC Grade – All Cycles					
	TAS-102 (N=533)			Placebo (N=265)		
Abnormality	N[a]	Grade 3 n (%)	Grade 4 n (%)	N[a]	Grade 3 n (%)	Grade 4 n (%)
Leukopenia	528	98 (18.6)	15 (2.8)	263	0	0
Neutropenia	528	140 (26.5)	60 (11.4)	263	0	0
Lymphocytopenia	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]
Thrombocytopenia	528	24 (4.5)	3 (0.6)	263	0	1 (0.4)

[a] Number of patients with a baseline and at least 1 post-baseline assessment during treatment.
[b] There is no CTC Grade 4 for anaemia based on laboratory data only.
[c] One adverse event of Grade 4 anaemia was reported (Source: TPU-TAS-102-301, Table 14.3.3.1).
Source: TPU-TAS-102-301, Table 14.3.14.2.

Median time to recovery in patients receiving TAS-102 were 28 days (range 1-217) for haemoglobin, 8 days for neutrophils (range 1-56), and 15 days (range 1-30) for platelets.

Serum chemistry abnormalities were equally distributed between the TAS-102 group and the placebo group. Serum glucose increase Grade 3 elevations in glucose were more frequently observed in the TAS-102 group (6.2%) compared to (2.4%) the placebo group, and is considered to be caused by an imbalance at baseline.

Safety in special populations

Renal impairment

Of the 533 patients in the RECOURSE study who received TAS-102, 306 (57%) patients had normal renal function (CLcr ≥90 mL/min), 178 (33%) patients had mild renal impairment (CLcr 60-89 mL/min), and 47 (9%) had moderate renal impairment (CLcr 30-59 mL/min), Patients with severe renal impairment were not enrolled in the study.

Table 53: Overview of Adverse Events by Baseline Renal Function – Estimated Glomerular Filtration Rate (AT Population). RECOURSE study

	Number (%) of Patients					
	TAS-102 (N=533)			Placebo (N=265)		
	Normal (eGFR ≥90 mL/min/ 1.73m^2) (N=334)	Mild Impairment (eGFR 60-89 mL/min/ 1.73m^2) (N=153)	Moderate Impairment (eGFR 30-59 mL/min/ 1.73m^2) (N=33)	Normal (eGFR ≥90 mL/min/ 1.73m^2) (N=160)	Mild Impairment (eGFR 60-89 mL/min/ 1.73m^2) (N=82)	Moderate Impairment (eGFR 30-59 mL/min/ 1.73m^2) (N=15)
Any adverse event (AE)	329 (98.5)	150 (98.0)	32 (97.0)	147 (91.9)	78 (95.1)	14 (93.3)
Any treatment-related AE	283 (84.7)	134 (87.6)	27 (81.8)	89 (55.6)	42 (51.2)	8 (53.3)
Any ≥Grade 3 AE	233 (69.8)	99 (64.7)	28 (84.8)	84 (52.5)	42 (51.2)	9 (60.0)
Any treatment-related ≥Grade 3 AE	155 (46.4)	77 (50.3)	20 (60.6)	16 (10.0)	7 (8.5)	3 (20.0)
Any serious AE (SAE)	99 (29.6)	42 (27.5)	14 (42.4)	56 (35.0)	27 (32.9)	5 (33.3)
Any treatment-related SAE	31 (9.3)	13 (8.5)	4 (12.1)	0	1 (1.2)	0

Source: Tables 14.3.4.9.2, 14.3.5.9.2, 14.3.6.9.2, 14.3.7.9.2, 14.3.8.9.2, 14.3.9.9.2.

In patients with moderate renal impairment, a higher incidence of ≥Grade 3 AEs and SAEs compared to the other 2 subgroups was observed in safety database group 2 receiving Lonsurf. The incidence of dose reductions was also increased in patients with renal impairment: based on baseline CLcr in 11.2%, 17.6%, and 23.9%, for normal, mild, and moderate renal impairment respectively. Also, drug interruptions occurred more frequently with moderate renal impairment: among patients in Safety Data Group 2 receiving Lonsurf, the incidence of drug interruption in normal, mild, and moderate group patients based on baseline CLcr was 28.7%, 26.7%, and38.8%, respectively. Cycle initiation delays of ≥8 days were observed in 69 of 314 (22.0%) patients with normal renal function, 57 of 179 (31.8%) patients with mild renal impairment, and 18 of 51(35.3%) patients with moderate renal impairment based on baseline CLcr.

Hepatic impairment

The pharmacokinetics of trifluridine and tipiracil hydrochloride have not been studied in patients with moderate or severe hepatic impairment. In RECOURSE, in the Lonsurf group, no marked safety differences were observed between patients with normal function and mild hepatic dysfunction. There were only 5 patients with moderate hepatic impairment (1 patient treated with TAS-102 and 4 patients on placebo).

Age

No particular concern exists for use in the elderly population, although a higher incidence and severity of blood and lymphatic disorders and cardiac events might be expected in the elderly population as compared to adult subjects. Patients 65 years of age or older who received Lonsurf had a higher incidence of the following events compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anaemia (26% vs 12%), Grade 3 or 4 leucopenia (26% vs 18%) and Grade 3 or 4 thrombocytopenia (9% vs 2%).

Table 54: Overview of Adverse Events by Age Group (AT Population)

	Number (%) of Patients			
	TAS-102 (N=533)		Placebo (N=265)	
	< 65 years (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)

Source: Tables 14.3.4.2, 14.3.5.2, 14.3.6.2, 14.3.7.2, 14.3.8.2, 14.3.9.2

In RECOURSE, only 45 patients were aged >75 years. In this particular subgroup of patients, AEs were more common than in patients ≥65 to <75 years and mainly included anaemia (46.7% vs. 40.2%), abdominal pain (20.0% vs. 14.1% constipation (22.2% vs. 12.9%), pyrexia (24.4% vs. 17.4%), hypoalbuminemia (8.9% vs. 2.5%), dizziness (8.9% vs. 3.3%), dyspnoea (17.8% vs. 7.5), and dry skin (8.9% vs 3.7%).

The review of AEs in the safety Data group 1 and 2 did not show emerging pattern in the incidence of events between the age groups except for cardiac events where an increase would be expected (see tables below).

Table 55: Adverse event profile for Elderly population (Group 1)

	TAS-102 N=761 n (%)				Placebo N=322 n (%)			
Years N	< 65 N=436	65-74 N=271	75-84 N=54	85+ N=1[a]	<65 N=181	65-74 N=112	75-84 N=29	85+ N=0
Total AEs	421 (96.6)	266 (98.2)	52 (96.3)		168 (92.8)	104 (92.9)	27 (93.1)	
Serious AEs	114 (26.1)	74 (27.3)	14 (25.9)		49 (27.1)	35 (31.3)	10 (34.5)	
Fatal	13 (3.0)	6 (2.2)	1 (1.9)		16 (8.8)	11 (9.8)	3 (10.3)	
Hospitalisation	110 (25.2)	71 (26.2)	13 (24.1)		47 (26.0)	33 (29.5)	10 (34.5)	
Life Threatening	8 (1.8)	7(2.6)	1 (1.9)		3 (1.7)	3 (2.7)	2 (6.9)	
Disability	2 (0.5)	0	0		0	1 (0.9)	0	
Other	3 (0.7)	6 (2.2)	1 (1.9)		0	0	0	
AEs leading to D/C	43 (9.9)	21 (7.7)	4 (7.4)		15 (8.3)	15 (3.4)	7 (24.1)	
Psychiatric	34 (7.8)	24 (8.9)	5 (9.3)		26 (14.4)	17 (15.2)	5 (17.2)	
Nervous	95 (21.8)	54 (19.9)	13 (24.1)		32 (17.7)	23 (20.5)	6 (20.7)	
Accident/injury	13 (3.0)	17 (6.3)	3 (5.6)		5 (2.8)	3 (2.7)	0	
Cardiac	12 (2.8)	13 (4.8)	4 (7.4)		5 (2.8)	7 (6.3)	0	
Vascular	42 (9.6)	18 (6.6)	4 (7.4)		16 (8.8)	10 (8.9)	3 (10.3)	
Cerebrovascular	No patients qualify				No patients qualify			
Infections and Infestations	108 (24.8)	72 (26.6)	14 (25.9)		25 (13.8)	20 (17.9)	4 (13.8)	
Anticholinergic syndrome	No patients qualify				No patients qualify			
Quality of life decreased [b]	11 (2.5)	8 (3.0)	2 (3.7)		10 (5.5)	4 (3.6)	2 (6.9)	
Sum of postural hypotension[c]	19 (4.4)	14 (5.2)	7 (13.0)		4 (2.2)	4 (3.6)	1 (3.4)	
Other AEs in elderly [d]	-	-	-	-	-	-	-	-

[a] One patient was older than 85 years of age and was included in the 75-84 subgroup.
[b] PTs used for this category were performance status decreased and general physical health deterioration.
[c] Combined terms: Orthostatic Hypotension, Falls, Black-Outs, Syncope, Dizziness, Ataxia, Fractures
[d] No additional adverse events of interest were identified for the elderly population.
Source: Table 54.1, Table 54.5, Table 54.7, Table 54.9, Table 54.11, Table 54.13, Table 54.16, Table 54.17, Table 54.18, Table 54.19, and Table 54.20.

Table 56: Adverse event profile for Elderly population (Group 2)

	TAS-102 N=646 n (%)				Placebo N=322 n (%)			
Years N	< 65 N=360	65-74 N=241	75-84 N=45	85+ N=0	< 65 N=181	65-74 N=112	75-84 N=29	85+ N=0
Total AEs	352 (97.8)	238 (98.8)	45 (100)		168 (92.8)	104 (92.9)	27 (93.1)	
Serious AEs	96 (26.7)	69 (28.6)	14 (31.1)		49 (27.1)	35 (31.3)	10 (34.5)	
Fatal	12 (3.3)	5 (2.1)	1 (2.2)		16 (8.8)	11 (9.8)	3 (10.3)	
Hospitalisation	93 (25.8)	66 (27.4)	13 (28.9)		47 (26)	33 (29.5)	10 (34.5)	
Life Threatening	7 (1.9)	6 (2.5)	1 (2.2)		3 (1.7)	3 (2.7)	2 (6.9)	
Disability	2 (0.6)	0	0		0	1 (0.9)	0	
Other	3 (0.8)	4 (1.7)	1 (2.2)		0	0	0	
AE Leading to Discontinuation	35 (9.7)	19 (7.9)	4 (8.9)		15 (8.3)	15 (13.4)	7 (24.1)	
Psychiatric	31. (8.6)	20 (8.3)	4 (8.9)		26 (14.4)	17 (15.2)	5 (17.2)	
Nervous	77 (21.4)	52 (21.6)	11 (24.4)		32 (17.7)	23 (20.5)	6 (20.7)	
Accident/injury	11 (3.1)	16 (6.6)	3 (6.7)		5 (2.8)	3 (2.7)	0	
Cardiac	10 (2.8)	12 (5.0)	4 (8.9)		5 (2.8)	7 (6.3)	0	
Vascular	38 (10.6)	16 (6.6)	3 (6.7)		16 (8.8)	10 (8.9)	3 (10.3)	
Cerebrovascular	No patients qualify				No patients qualify			
Infections and Infestations	91 (25.3)	67 (27.8)	13 (28.9)		25 (13.8)	20 (17.9)	4 (13.8)	
Anticholinergic syndrome	No patients qualify				No patients qualify			
Quality of Life decreased [a]	11 (3.1)	8 (3.3)	2 (4.4)		10 (5.5)	4 (3.6)	2 (6.9)	
Sum of postural hypotension [b]	14 (3.9)	13 (5.4)	5 (11.1)		4 (2.2)	4 (3.6)	1 (3.4)	
Other in elderly [c]								

[a] : PTs used for this category were performance status decreased and general physical health deterioration.
[b] Combined terms: Orthostatic Hypotension, Falls, Black-Outs, Syncope, Dizziness, Ataxia, Fractures
[c] No additional events of interest were identified for the elderly population.
Source: ISS Table 14.3.6.1 and ISS Table 14.3.10.1; Table 54.8, Table 54.10, Table 54.12, Table 54.14, Table 54.22, Table 54.23, Table 54.24, Table 54.25, and Table 54.26.

Radiotherapy

There was a slightly higher incidence of overall haematological and myelosuppression-related adverse reactions for patients who received prior radiotherapy compared to patients without prior radiotherapy in RECOURSE (54.6% versus 49.2%, respectively), of note febrile neutropenia was higher in Lonsurf-treated patients who received prior radiotherapy vs. those who did not.

Safety related to drug-drug interactions and other interactions

Intrinsic Factors

Gender

In female patients receiving TAS-102 group in Safety Data Group 2, AEs that were reported more than in men included anaemia (36.7% vs 31.3%), abdominal pain (19.1% vs 13.3%), abdominal pain upper (10.2% vs 3.6%), nausea (58.6% vs 46.4%), vomiting (41.0% vs 20.8%), and cough (13.3% vs 7.4%). Anaemia (9.2% vs 5.2%), abdominal pain (15.4% vs 13.5%, abdominal pain upper 3.8% vs 3.6%, nausea 31.5% vs 19.8%,

vomiting 23.1% vs 11.5%, and cough 12.3% vs 8.9% were also more frequently observed in the placebo group. Female patients in the TAS-102 group had also a higher incidence of grade 3-4 neutropenia than male patients; this abnormality was not observed in the placebo group .

ECOG performance status

In both TAS-102 and placebo groups in safety group 2, ≥Grade 3 AEs and serious AEs were more frequent for patients with PS=1-2 at baseline compared to those with PS=0 at baseline. AE which were more reported in the ECOG 1/2 group than in the ECOG 0 group receiving TAS-102 were vomiting (31.9% vs 26.5%) and oedema peripheral (13.6% vs 8.0%), but a difference was also reported in the placebo group.

Race

Grade 3 or higher AE were reported in 70,5% of Caucasians/Whites, 75% (n=4) of African Americans , and 67.6% of Asians patients receiving TAS-102. In the placebo group, grade 3 or higher AE were less reported in Asians (36.4%), compared to Caucasians/Whites (51.9%) and African Americans (60.0%, n=5). It should be noted that few data exists in the African American population.

Extrinsic Factors

Drug Interactions

The effect of food on PK of TAS-102 was investigated in Study J004-10040040, a single-center, open-label, 2-group, 2-period crossover, PK study of TAS-102 administered to patients with solid tumours. The patients received single doses of TAS-102 (35 mg/m2) under two conditions, assigned in random order: fasting condition and after a meal. Sixteen patients were enrolled in the study, and 14 patients were included in the evaluation of the food effect. The results showed that food consumption did not affect the AUC of FTD, but reduced the Cmax of FTD and the Cmax and AUC of TPI by about 40%. The AUC of FTD, the antitumor component of TAS-102, was generally the same between fed and fasting states; a possible decrease in exposure to FTD and TPI due to food consumption was considered unlikely to affect the efficacy of TAS-102.

However, a significant correlation between the increase in the Cmax of FTD and the decrease in neutrophil counts, observed in the dose-finding study of TAS-102 conducted in Japan (Study J001-10040010), suggests that TAS-102 should be administered in a fed state in which the Cmax is lower, rather than in a fasting state.

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

Geographical region

Analysis of safety data by geographic region was performed for Safety Data Group 2. In both treatment groups, treatment-related AEs were more frequent in Japanese patients than in US/EU/Australia patients, and SAEs were more frequent in US/EU/Australia patients than in Japanese patients.

Discontinuation due to adverse events

Discontinuation of treatment

In the RECOURSE study, 3.6% of patients in the TAS-102 group and 1.5% of patients in the placebo group had adverse event/SAE indicated as the primary reason for discontinuation of study treatment based on the treatment discontinuation page of the eCRF. The most frequent AEs leading to discontinuation in the TAS-102 group (at least 3 patients) were general physical health deterioration (2.3% of patients), fatigue (1.1%) and dyspnoea (0.6%); while in the placebo group, the most frequent AEs leading to discontinuation (at least 3 patients) were blood bilirubin increased (2.3%), general physical health deterioration (1.9%), ascites (1.9%), decreased appetite (1.5%), hepatic failure (1.1%), abdominal pain (1.1%) and asthenia (1.1%). All other AEs leading to DC were reported for 2 or fewer patients in either group.

Dose reduction

In the RECOURSE study, 73 (13.7%) patients in the TAS-102 group had at least 1 dose reduction during treatment. Adverse events leading to dose reduction were reported for 72 of these patients. The most frequent AEs leading to dose reduction in the TAS-102 group were: neutropenia (17, 3.2%), anaemia (11, 2.1%), neutrophil count decreased (10, 1.9%), febrile neutropenia (10, 1.9%), fatigue (8, 1.5%), and diarrhoea (7, 1.3%). In the placebo group, 3 (1.1%) patients had a single dose reduction, with 2 reporting AEs leading to dose reduction (1, anaemia; 1, bronchopneumonia). Across all cycles, 289 (54.2%) patients in the TAS-102 group had AEs that resulted in interruptions in dosing, dose delays and/or dose reductions compared to 36 (13.6%) patients in the placebo group.

Dose interruption or delay

In terms of dose delays, cycles delayed ≥4 days were more frequently reported for TAS-102 than placebo (52.6% vs. 6.5%). In the TAS-102 group, the most frequent AEs leading to interruptions/delays and/or dose reductions were: neutrophil count decreased (109, 20.5%), neutropenia (106, 19.9%), and anaemia (29, 5.4%). In the placebo group, the most frequent AEs leading to these outcomes (in at least 3 patients) were: decreased appetite (5, 1.9%) and pyrexia (3, 1.1%).

2.6.1. Discussion on clinical safety

Overall, the safety profile of TAS-102 (Lonsurf) was consistent across studies and is attributable to the antineoplastic agent trifluridine and typical for a myelosuppressive agent: haematological toxicity was most prominent in the pivotal RECOURSE study.

The safety profile of TAS-102, with mainly bone marrow related and GI related AEs, appears predictable, manageable and well tolerated by the heavily pretreated target population. According to the RECOURSE study protocol, patients were selected on the basis of lack of significant hepatic or renal co-morbidities, CNS metastases, cardiac disease, uncontrolled hypertension and diabetes mellitus and gastrointestinal haemorrhage. Also, only patients with ECOG 0 or 1 performance status were allowed to be enrolled in the pivotal study.

RECOURSE Study

At the time of the non-survival data cut-off (31-January-2014), the majority of patients (n=759, 95.1%) had discontinued treatment, and 39 patients (37 and 2, in the TAS-102 and placebo groups, respectively) continued on treatment.

The main reason for discontinuation in both groups was (clinical/radiological) disease progression. The proportion of patients discontinuing due to AEs was in general low, with a higher percentage of patients discontinuing in the TAS-102 group.

The most frequent reason for dose reduction and/or cycle delays in the TAS-102 treated patients were haematological-related AES. Data provided are within the expected range and show an increased incidence of AEs and G3/4 haematological AEs in patients previously exposed to RT or who received more lines of prior chemotherapy regimens. Given the overall low rate of treatment discontinuations, haematological events appear well tolerated and manageable in clinical practice.

Despite the high incidence of dose delays, there was very little difference (2%) between the number of cycles initiated and completed, indicating good tolerability and no evidence for cumulative toxicity.

The most common treatment-related AEs for the Lonsurf-treated patients were: nausea, anaemia, decrease appetite, fatigue, diarrhoea, neutropenia, neutrophil count decreased, vomiting, and WBC count decreased, all

of them reported in >20% patients. The frequency of hematologic impairment-related AEs, primarily neutropenia, anaemia, leucopenia, and thrombocytopenia associated with myelosuppression, was much higher in the Lonsurf group (70.9%) than in the placebo group (15.5%).

Haematological toxicity is considered an expected AE for this class of products. The clinical management of these toxicities, in terms of dose adjustments and/or the use of supportive haematological therapies have been adequately provided by the Applicant.

Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor toxicity, but at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is < 1.5 x10^9/L, if the platelet counts are < 75x 10^9/L, or if the patient has an unresolved Grade 3 or 4 non-haematological clinically relevant toxicity from prior therapies.

Serious infections have been reported following treatment with Lonsurf (see section 4.8). Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated. In the RECOURSE study, 9.4% of patients in the Lonsurf group received G-CSF mainly for therapeutic use (see section 4.4 of the SmPC).

GI events were commonly observed with the administration of Lonsurf. The degree of emetogenicity attributed to Lonsurf is substantial. Considering the health and QoL impact of nausea and vomiting, even of further magnitude in this advanced disease setting, instructions for preventive measurements have been adequately reflected. Patients with nausea, vomiting, diarrhoea and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrhoeal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary (see sections 4.2 and 4.4 of the SmPC).

Overall, the safety profile of Lonsurf seems to be generally in line with that of a thymidine nucleotide analogue. The main differences observed were that mucositis (reported as "mucosal inflammation" or "stomatitis", respectively 5.6% and 7.9% for Lonsurf and 4.5% and 6.0% for placebo) and hand-foot syndrome adverse events (2.3% in both treatment groups), were reported with lower incidence that those found in the literature (up to 50%). Most of the events were grade 1-2 (<1% grade >3 in Lonsurf, 0% placebo).

As for maximum CTC grade, the majority (78.4%) of Lonsurf patients experienced AEs of maximum grade ≤3 (28.9% Grade 1-2, 49.5% Grade 3), with anaemia (15.9%), neutropenia (13.7%), neutrophil count decreased (11.8%), and WBC count decrease (9.2%) as the most commonly reported grade 3 events and neutropenia (6.4%) and neutrophil count decreased (4.1%) as the most frequent grade 4 AEs.

In both treatment groups, frequencies of treatment-related AEs followed similar trends to those observed for all causality AEs, with a higher percentage of treatment-related AEs in the Lonsurf group than the placebo group (85.7% vs. 54.7%, respectively). Grade ≥3 treatment-related AEs were also more frequent for Lonsurf patients (49.0% vs. 9.8% in the placebo group).

In the pivotal RECOURSE study the number of patients receiving the target dose of Lonsurf administered decreases with the number of cycles. Although it is observed that dose interruptions in the Lonsurf group occurred more frequently in the second or subsequent cycles, suggesting late or cumulative toxicity, the median relative dose intensity was still 91.2% in the Lonsurf group and only 3.4% of patients discontinued treatment, suggesting that the proposed dosing regimen is manageable.

The most common reason for treatment discontinuation was progression of disease and although the number of patients who discontinued Lonsurf due to AE/SAE was higher in the Lonsurf group (3.4%) than in the placebo group (1.6%), the absolute numbers are low.

From safety database group 2 data, the most frequently reported treatment-related AEs were anaemia, neutropenia, neutrophil count decreased, decreased appetite, and WBC count decreased and nausea.

Safety data group 1 and 2 were generally in line, including exposure and reasons for discontinuation.

Special populations

No marked safety differences were observed between patients with normal function and mild hepatic dysfunction. In patients with moderate renal impairment, a higher incidence of ⩾Grade 3 AEs, SAEs, incidence of dose reductions and, drug interruptions were observed. In addition, a higher exposure of trifluridine and tipiracil was observed in patients with moderate renal impairment, compared with patients with normal renal function or patients with mild renal impairment. Patients with moderate renal impairment should be more frequently monitored for haematological toxicities (see sections 4.4 and 5.2 of the SmPC).

It is however agreed that no dose adjustments can be recommended for patients with mild to moderate renal impairment for the time being Patients with severe renal impairment were not enrolled in the RECOURSE study. Lonsurf is therefore not recommended for use in patients with severe renal impairment or end-stage renal disease.

A study in patients with renal impairment is ongoing and study results will be submitted by December 2017 (see RMP).

Lonsurf is not recommended for use in patients with moderate or severe hepatic impairment (National Cancer Institute [NCI] Criteria Group C and D) as Lonsurf has not been studied in these patients (see section 4.4 of the SmPC). A study in patients with hepatic impairment is ongoing and study results will be submitted by December 2017 (see RMP).

In the Lonsurf group, AEs were more frequently reported in patients >65 years than in patients <65 years of age and mainly included anaemia, neutropenia, neutrophil count decreased, platelet count decreased, and white blood cell count decreased. The data in patients >75 years are limited but do suggest higher toxicity. Since an a priori decrease in dose could potentially negatively impact efficacy and the difference in toxicity is not considered significant, no adjustment of the starting dose is required in patients ⩾ 65 years old (see sections 4.2, 4.8, 5.1 and 5.2 of the SmPC).

AEs were more frequent in Japanese patients than in US/EU/Australia patients, and SAEs were more frequent in US/EU/Australia patients than in Japanese patients, which might be due to differences in reporting. AEs were equally distributed among races. There is limited data on Lonsurf in Black/African American patients but there is no biological rationale to expect any difference between this subgroup and the overall population (see section 4.2 of the SmPC).

AEs Grade ≥3 and serious AEs were more frequently reported in patients with ECOG PS1-2 at baseline compared to those with PS=0 at baseline. AE which were more reported in the ECOG PS1-2 group than with PS=0 group receiving TAS-102 were vomiting (31.9% vs 26.5%) and oedema peripheral (13.6% vs 8.0%), but a difference was also reported in the placebo group.

Lonsurf had no clinically relevant effect on QT/QTc prolongation compared with placebo in an open label study in patients with advanced solid tumours.

There are no data available on the effects of Lonsurf on human fertility. There are no available data from the use of Lonsurf in pregnant women. Based on the mechanism of action, trifluridine is suspected to cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity. Lonsurf should not be used during pregnancy unless the clinical condition of the woman requires treatment with Lonsurf (see sections 4.6 and 5.3 of the SmPC).

The highest dose of Lonsurf administered in clinical trials was 180 mg/m^2 per day. The adverse drug reactions reported in association with overdoses were consistent with the established safety profile. The primary anticipated complication of an overdose is bone marrow suppression. There is no known antidote for an overdose of Lonsurf. Medical management of an overdose should include customary therapeutic and supportive medical intervention aimed at correcting the presenting clinical manifestations and preventing their possible complications (see section 4.9 of the SmPC).

Since Lonsurf contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 4.4 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of TAS-102 (Lonsurf) was consistent across studies and is attributable to the antineoplastic agent trifluridine and typical for a myelosuppressive agent: haematological toxicity was most prominent in the pivotal RECOURSE study. Nausea and vomiting were reported frequently and it should be questioned whether patients adequately received supportive therapies. Overall, the toxicity related to TAS-102 treatment appears to be manageable, and seems, in some aspects such as the absence of mucositis to be better tolerable than fluoropyrimidines. More data on safety in patients with renal and hepatic impairment are awaited.

2.7. Risk Management Plan

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

The PRAC considered that the RMP version 1.0 (dated 18 February 2015) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment reports dated 09 July 2015, 11 November 2015 and 11 February 2016.

The CHMP implemented this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 4.0 (dated 15 February 2016) with the following content:

Table 57. Summary of Safety concerns

Important identified risks	Bone marrow suppression Gastrointestinal symptoms (nausea, vomiting, diarrhoea) Infection Use in patients with moderate renal impairment
Important potential risks	Developmental toxicity/Use in pregnant and breast feeding women
Important missing information	Use in patients with moderate to severe hepatic impairment Use in patients with severe renal impairment Use in patients with cardiac disorders Use in patients in a worse condition than ECOG 0-1.

Pharmacovigilance plan

Table 58. On-going and planned additional PhV studies/activities in the PhV Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
TO-TAS-102-107: A phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of renal impairment. Category 3	Compare PK profile and assess safety and tolerability of TAS-102 in patients with advanced solid tumours (except breast cancer) and varying degrees of renal impairment. PK parameters will be compared for patients with normal renal function and those with renal impairment. The first part of the study will be followed by an extension part aiming to further assess the safety and tolerability of TAS-102 in this population of patients.	Safety in patients with renal impairment	Ongoing	December 2017

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
TO-TAS-102-106: A phase I, open-label study to evaluate the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment. Category 3	Compare the plasma PK profile of TAS-102 (FTD, FTY, and TPI) in patients with advanced solid tumours and varying degrees of hepatic impairment in order to evaluate the impact of hepatic impairment on the PK profile of TAS-102 (FTD and TPI) and FTY (the major metabolite of FTD). An Exploratory Objective (Cycles 2 and beyond) is to assess the safety and tolerability of TAS-102 in patients with advanced solid tumours and varying degrees of hepatic impairment in Cycles 2 and beyond.	Safety in patients with hepatic impairment	Ongoing	Final report Dec 2017

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are specific obligations
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure the effectiveness of risk minimisation measures)

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Bone marrow suppression (identified risk)	Wording in Section 4.2 of the SmPC (*Recommended dose adjustments),4.4, 4.8.* Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Gastrointestinal symptoms (identified risk)	Wording in Section 4.4 of the SmPC, 4.8 Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Infection (identified risk)	Wording in Section 4.2 of the SmPC (Recommended dose adjustments), 4.4, 4.8 Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	patients.	
Use in patients with moderate renal impairment (identified risk)	Wording in Section 4.4 of the SmPC, 5.2 Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Developmental toxicity/Use in pregnant and breast feeding women (potential risk)	Wording in Section 4.6 of the SmPC, 5.3 Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Use in patients with moderate to severe hepatic impairment (missing information)	Wording in Section 4.4 of the SmPC, 5.2. Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Use in patients with severe renal impairment (missing information)	Wording in Section 4.4 of the SmPC, 5.2. Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Use in patients with cardiac disorders (missing information)	Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None
Use in patients in a worse condition than ECOG 0-1	Wording in SmPC Section 5.1 Prescription only medicine. Use restricted to physicians experienced in chemotherapy treatment in cancer patients.	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lonsurf (trifluridine / tipiracil) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

A statistically significant improvement in OS with TAS-102 plus BSC (7.2 months) compared with placebo plus BSC (5.2 months) has been observed in the pivotal RECOURSE study. The hazard ratio for death (TAS-102 versus placebo) was 0.69 (95% CI, 0.59-0.81; p<0.001). The 1-year overall survival rates were 27% and 17% respectively. The 2 months gain in median OS associated to treatment with TAS-102 appears to be of clinical relevance considering the lack of subsequent therapies and the poor prognosis of this patient population. The investigator-assessed PFS results appear to support the OS data (secondary endpoint). Treatment with TAS-102 decreased the risk of death by 31% compared with placebo (HR 0.69 [95% CI: 0.59, 0.81], and 1- and 2-sided p<0.0001, stratified log-rank test).

Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favourable across the stratification groups (KRAS status, time since diagnosis of 1st metastasis, and geographical region) and all pre-specified subgroups. This effect was further substantiated by the results of the key secondary efficacy endpoint: PFS HR=0.48, 95% CI: 0.41-0.57, p<0.0001. Results obtained for other secondary efficacy endpoints (TTF, ORR, DCR and DR) were also supportive.

Uncertainty in the knowledge about the beneficial effects.

Unfortunately the results of the biomarker analysis, which could potentially help in order to identify parameters for patient selection, have not been provided for the pivotal RECOURSE study. In the phase II Japanese Study J003-10040030 the expression of TK and TPase proteins were not related to efficacy endpoints (DCR, PFS and OS) in either group. MSI status and TK1 as possible biomarkers will be further explored in a selected Japanese subpopulation from the phase III RECOURSE study. The included population is the most favourable within the generally unfavourable late stage mCRC having failed several prior chemotherapy regimens (e.g. ECOG PS=0-1 patients). Another limitation is the limited characterisation of Lonsurf in the elderly population. However, the effect of TAS 102 on overall survival was similar in patients <65 years and ≥65 years of age.

Risks

Unfavourable effects

Overall, the safety profile of TAS-102 was consistent across studies and is attributable to the antineoplastic agent trifluridine and typical for a myelosuppressive agent: in addition to gastrointestinal AEs haematological toxicity was most prominent in the pivotal RECOURSE study.

The most frequently reported treatment-related AEs were anaemia, neutropenia, neutrophil count decreased, decreased appetite, and WBC count decreased and nausea. In the pivotal RECOURSE trial, the frequency of haematologic impairment-related AEs, primarily neutropenia, anaemia and other events associated with myelosuppression, was much higher in the TAS-102 group (70.9%) than in the placebo group (15.5%).

Treatment related anaemia was more frequently reported for TAS-102 (31.3% (grade ≥3, 12.2%)) than for placebo (4.5 (grade ≥3 1.9). Patients with higher trifluridine exposure had an increased risk of Grade ≥3 neutropenia. These events were generally manageable with reductions in dose, delays in cycle initiation and occasional use of G-CSF (9.4% of patients receiving TAS-102). Three (0.5%) patients died due to fatal infections related to TAS-102.

GI events were commonly observed with the administration of TAS-102. Treatment related diarrhoea, nausea and vomiting were commonly reported and occurred more frequently in the TAS 102 group than in the placebo group.

No effect of TAS-102 on QTc prolongation or other cardiac events have been observed. Thromboembolic events (TEEs) were more frequent in the TAS-102 group (3.7%) compared to the placebo group (1.9%).

Treatment-related SAEs were reported for 9.8% of patients in the TAS-102 group and 0.6% of patients in the placebo group. Most common treatment related SAEs for TAS-102 were febrile neutropenia and anaemia.

Overall, the safety profile of TAS-102 seems to be generally in line with that of a thymidine nucleotide analogue. Renal impairment-related AEs (all grades) were more frequent in the TAS-102 group than placebo (9.0% vs. 4.9%, respectively). Considering the advanced stage of the intended target population, any deleterious effect on renal function is considered relevant, especially due to potential toxicity implications. Adequate information on the monitoring/management of these events has been included in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

An important limitation of the safety database is the short median duration of follow-up of patients treated with TAS-102.

In patients with moderate renal impairment, a higher incidence of Grade ≥ 3 AEs and SAEs was observed. A

study in patients with renal impairment is ongoing and study results are awaited. In the meantime, no specific dose recommendation for patients with mild to moderate renal impairment is warranted.

Effects table

Table 59: Effects Table for Lonsurf: treatment of adult patients with metastatic colorectal cancer (CRC)

Effect	Short Description	Unit	Lonsurf 35mg/m²/dose BID	Control
Favourable Effects				
OS	Primary endpoint	Median (months)	7.2 95% CI (6.6, 7.8)	5.2 95% CI (4.6, 5.9)
			HR 95% CI: 0.69 (0.59, 0.81) p<0.0001	
PFS	2ndary endpoint	Median (months)	2.0 95% CI (1.9, 2.1)	1.7 95% CI (1.7, 1.8)
			HR 95% CI: 0.48 (0.41, 0.57) p<0.0001	
ORR	2ndary endpoint	Number (%)	8 (1.6%), 95% CI (0.7, 3.1) CR= 0 (0.%) vs PR = 8 (1.6%)	1 (0.4%), 95% CI (0.0, 2.1) CR= 1 (0.4%) vs PR = 0 (0%)
Unfavourable Effects				
Nausea		Proportion	AE 48.4% G3/4 1.9% SAE 0.6%	AE 23.8% G3/4 1.1% SAE 0.0%
Anemia		Proportion	AE 40.2% G3/4 16.1% SAE 1.9%	AE 8.3% G3/4 2.6% SAE 0.0%
Fatigue		Proportion	AE 35.3% G3/4 3.9% SAE 0.6%	AE 23.4% G3/4 5.7% SAE 0.0%
Diarrhoea		Proportion	AE 31.9% G3/4 3.0% SAE 0.8%	AE 12.5% G3/4 0.4% SAE 0.0%
Neutropenia		Proportion	AE 29.3% G3/4 20.1% SAE 0.8%	AE 0.0% G3/4 0.0% SAE 0.0%
Vomiting		Proportion	AE 27.8% G3/4 2.1% SAE 1.3%	AE 14.3% G3/4 0.4% SAE 0.0%
neutrophil count decreased		Proportion	AE 27.8% G3/4 15.9% SAE 0.0%	AE 0.4% G3/4 0.0% SAE 0.0%
WBC decreased		Proportion	AE 27.4% G3/4 10.3% SAE 0.2%	AE 0.4% G3/4 0.0% SAE 0.0%

Effect	Short Description	Unit	Lonsurf 35mg/m^2/dose BID	Control
Tolerability			AE 98.3% ≥1dose reduction: 13.7% ≥1dose delay: 52.6% AE leading to discontinuations 34.5% G3/4 27.3%	AE 93.2% ≥1dose reduction: 1.1% ≥1dose delay: 6.5% AE leading to discontinuations 11.1% G3/4 8.3%

Benefit-risk balance

Importance of favourable and unfavourable effects

The efficacy results of the pivotal RECOURSE study are considered of clinical relevance. A statistically significant improvement in OS (HR 0.69) associated with treatment with TAS-102 compared with placebo, and supported by a statistically significant improvement in PFS (HR 0.48) is observed. The gain in median OS is 2.0 months, whereas the median improvement in PFS consists of a few weeks at best (formally the difference in median PFS between treatment arms was only 0.3 months). However, such subgroup has not been identified so far. Symptom-related endpoints and quality of life scores are not available, but dose reductions, dose interruptions, or discontinuations were not excessively frequent.

The toxicity profile of TAS-102 is more or less comparable with fluoropyrimidines and typical for a myelosuppressive agent. In addition to gastrointestinal AEs, haematological toxicity was most prominent; the limited occurrence of mucositis in patients receiving TAS-102 is considered favourable. Overall, the safety issues with TAS-102 are manageable, although it is questioned whether patients were adequately supported with anti-emetics, due to the high incidence of nausea and vomiting. Additional recommendations for prevention and management have been addressed in the SmPC. Other toxicities frequently associated with this class of product (e.g. mucositis, and hand-foot syndrome) which are known to have a major impact on patient´s QoL, were reported with low frequency. This is particularly relevant in the context of non-curative therapy for an end-stage disease.

Benefit-risk balance

The benefit of TAS-102 in terms of OS needs to be weighed against observed drug-related toxicity, in particular haematological toxicity and GI-symptoms like diarrhoea, nausea and vomiting. While these are significant AEs that affect quality of life, the majority of these events were mild to moderate, had limited impact on treatment continuity, and were generally treated without requiring hospitalisation. Overall, the safety issues were manageable. Therefore, the benefit-risk is considered positive.

Discussion on the benefit-risk balance

For patients whose colorectal cancer has been treated with, and has proven refractory to, fluoropyrimidines, oxaliplatin, irinotecan, an anti-VEGF therapy, and an anti-EGFR inhibitor in case of KRAS wild-type tumours, therapeutic options that provide overall survival or clinical benefit remain limited. Current National Comprehensive Cancer Network (NCCN) guidelines list three options: regorafenib, participation in a clinical trial or best supportive care.

Although no direct comparison has been performed, the efficacy shown by TAS-102 can be considered in line with that obtained with regorafenib, recently authorised for use in a similar setting. The safety profile of Lonsurf is distinct from that of regorafenib. Unfortunately, comparative data are lacking since regorafenib was not

licensed at the time of clinical evaluation of Lonsurf.

The subgroup analyses in RECOURSE presented so far did not identify a subgroup benefitting most from the treatment on the basis of tumour characteristics. No biomarker analyses have been provided in RECOURSE. The Applicant is recommended to provide data from the ongoing study in selected Japanese subpopulation from the phase III RECOURSE study regarding MSI status, TK1 protein expression and other biomarkers which may also be relevant.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lonsurf in the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the review of data, the CHMP considered that the active substance tipiracil hydrochloride was to be qualified as a new active substance.