Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for trifluridine / tipiracil

Proprietary Product Name: Lonsurf and Orcantas

Sponsor: Servier Laboratories Australia Pty Ltd

June 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
5-FU	5-fluoruracil
ACM	Advisory Committee on Medicines
AE	Adverse event
AIHW	Australian Institute of Health and Welfare
AT	As treated (population)
AUC	Area under the curve
BCS	Biopharmaceutics Classification System
BD	Twice daily
BSA	Body surface area
BCS	Biopharmaceutics Classification System
BD	Twice daily
BSC	Best supportive care
CER	Clinical evaluation report
CI	Confidence interval
CHMP	Committee for Medicinal products for Human use
CL/F	Apparent 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

Abbreviation	Meaning
DR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
FDC	Fixed dose combination
FTD	Trifluridine
FTY	5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ITT	Intent to treat
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LV	Leucovorin
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Abbreviation	Meaning
OCT2	Organic cation transporter 2
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PO	Orally (per os)
PS	Performance status
PSC	Pharmaceutical Subcommittee
PT	Preferred term
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 Tumours
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TAS-102	Trifluridine-tipiracil
TDS	3 times daily
$T_{1/2}$	Terminal elimination half-life
TK1	Thymidine kinase 1
T_{max}	Time of maximum observed plasma concentration

Abbreviation	Meaning
Tpase	Thymidine phosphorylase
TPI	Tipiracil hydrochloride
TR	Tumour response (evaluable population)
TTF	Time to treatment failure
VEGF	Vascular endothelial growth factor
US	United States
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	19 May 2017
Date of entry onto ARTG	23 May 2017
ARTG numbers:	273238, 273239
Active ingredients:	Trifluridine/tipiracil
Product names:	Lonsurf and Orcantas
Sponsor's name and address:	Servier Laboratories Australia Pty Ltd 8 Cato Street Hawthorn East VIC 3123
Dose form:	Tablets: film-coated, unscored
Strengths:	15 mg / 6.14 mg 20 mg / 8.19 mg
Pack size:	Blister packs of 20 and 60 tablets
Approved therapeutic use:	Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.
Route of administration:	Oral
Dosage:	Cycle with 35 mg/m^2 twice daily (starting dose)

Product background

This AusPAR describes the application by the sponsor to register fixed dose combination (FDC) tablets containing 2 new chemical entities:

- Trifluridine is an antineoplastic, a thymidine based nucleoside analogue;
- Tipiracil is a thymidine phosphorylase inhibitor, included at half the molar amount of trifluridine. Tipiracil thus increases trifluridine systemic exposure.

The tablets are proposed for use in the treatment of metastatic colorectal cancer (mCRC). Proposed tradenames are Lonsurf and Orcantas. The proposed indication is:

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

Staging and natural history

Colorectal cancer (CRC) is the third most frequently diagnosed cancer worldwide. In Australia, the projected incidence of colorectal cancer was 17,520.[1] Data from the Australian Institute of health and Welfare (AIHW) show that colorectal cancer is the second most commonly diagnosed cancer in both males and females in Australia. It is also listed the second most common cause of death from cancer.[1] Patients with unresectable mCRC usually die from the disease, with 5 year overall survival of about 15%. The primary chemotherapy for mCRC is a combined regimen containing a fluoropyrimidine such as 5-fluoruracil (5-FU) or capecitabine, along with other agents such as leucovorin (LV), irinotecan and oxaliplatin.

For patients with refractory mCRC, the best way to combine and sequence the available drugs to optimise treatment has not yet been established. In general, current clinical advice states that exposure to all active drugs, as appropriate, is more important than the specific sequence of administration. Further, the choice of regimen (particularly the cytotoxic chemotherapy backbone) is also influenced by the goals of chemotherapy, which differ according to the clinical scenario.[2]

For patients with refractory mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan based chemotherapy, and anti-VEGF agent, and (if RAS wild type) an anti-EGFR agent and who require additional therapy, current clinical practice advice include the use of single agent regorafenib (Stivarga), if performance status is adequate.[2]

Trifluridine and tipiracil hydrochloride

This submission is for a proposed fixed dose combination oral cytotoxic tablet containing trifluridine (FTD) and tipiracil hydrochloride (TPI). Trifluridine-tipiracil is referred to as TAS-102 within the CER and submission dossier.

Trifluridine (FTD) is an antineoplastic thymidine-based nucleoside analog that inhibits thymidylate synthase and, after modification within tumour cells, is incorporated into DNA, causing strand breaks.

Tipiracil (TPI) is a potent thymidine phosphorylase inhibitor, which inhibits trifluridine metabolism by inhibiting thymidine phosphorylase (TPase), thus increasing systemic exposure to FTD when FTD and TPI are given together. Tipiracil also has antiangiogenic properties.

Regulatory guidelines

The following European Medicines Agency (EMA) guidelines, which have been adopted by the TGA, are considered relevant to the current application:

- Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4).

[1] Australian Institute of Health and Welfare (AIHW). Cancer In Australia, an overview, 2014. Australian Government.
[2] Clark JW, et al. Metastatic Colorectal Cancer. UpToDate Online Article. Updated 3rd Jan 2017.

- Points to consider on application with 1) Meta-analyses; 2) One pivotal study (EMA/CPMP/EWP/2330/99).
- Guideline on the clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1).

Regulatory status

This is the first submission to register the proposed fixed dose trifluridine/tipiracil tablet formulation in Australia. The regulatory status at the time of this submission to TGA is outlined below. The sponsor pointed out that at the time of submission to TGA, no application for the proposed product had been rejected, withdrawn or repeatedly deferred in Europe or Canada.

Japan; Pharmaceuticals and Medical Devices Agency (PMDA)

The first overseas registration for trifluridine/tipiracil was in Japan on 24 March 2014. The medicine has been marketed in Japan as Lonsurf since 26 May 2014.

A condition for approval in Japan included the submission of the results of the ongoing Phase III study to confirm the efficacy and safety of the product in patients with unresectable advanced or recurrent colorectal cancer. The PMDA also stated that:

> *'The occurrence of bone marrow suppression and infections needs to be further investigated via post-marketing surveillance.'*

United States of America (USA); Food and Drug Administration (FDA)[3]

Lonsurf was approved by the US FDA on 22 September 2015 for the following indication:

> *'Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.'*

At the time of writing this overview, the approved Product Information (PI) document for the US was dated September 2015. The application for Lonsurf was not referred to an FDA advisory committee. The Lonsurf approval letter states that this was because the safety profile is acceptable for the treatment of patients with unresectable advanced or recurrent colorectal cancer. The application did not raise significant public health questions on the role of Lonsurf for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from an advisory committee discussion.

FDA determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the *Federal Food, Drug and Cosmetic Act* (DCA) will not be sufficient to assess signals of a serious risk of impaired hepatic and renal function on the pharmacokinetics of Lonsurf (trifluridine and tipiracil) resulting in excessive toxicity to include myelosuppression. FDA determined that the following post-market requirements were appropriate:

- Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with moderate to severe hepatic impairment. Expected final report submission date of December 2017.

[3] Checked 9 January 2017.

- Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with severe renal impairment. Expected final report submission date of December 2017.

European Union (EU); European Medicines Agency (EMA)[3]

Lonsurf was approved by the EMA on 25 April 2016 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 chemotherapies, anti-VEGF agents, and anti-EGFR agents.'*

The Committee for Medicinal products for Human use (CHMP) reviewed the data on quality, safety and efficacy. The CHMP considered by consensus that the risk-benefit balance of Lonsurf in the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents, is favourable.

In the EU, Lonsurf is subject to additional monitoring and is labelled with a black triangle encouraging healthcare professionals and patients to report any suspected adverse reactions.

Switzerland; Swiss Agency for Therapeutic products (SwissMedic)[3]

An application for marketing approval was submitted in Switzerland on 23 February 2016. No update was available on the Swissmedic website.

Product Information

The PI approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 1: Regulatory timeline of this submission

Description	Date
Submission dossier accepted and first round evaluation commenced	2 May 2016
First round evaluation completed	31 October 2016
Sponsor provides responses on questions raised in first round evaluation	19 December 2016
Second round evaluation completed	16 January 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	24 February 2017
Sponsor's pre-Advisory Committee response	14 Mar 2017
Advisory Committee meeting	6 April 2017
Registration decision (Outcome)	19 May 2017
Completion of administrative activities and registration on ARTG	23 May 2017
Number of working days from submission dossier acceptance to registration decision*	232

* Legislative timeframe for standard applications is 255 working days (see *Therapeutic Goods Regulations 1990*); target timeframe is 220 working days.

III. Quality findings

Drug substances (active ingredient)

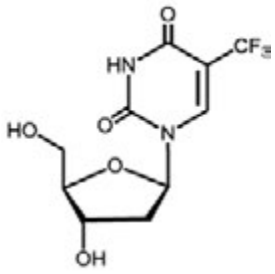
Trifluridine

Trifluridine is a synthetic drug which has not previously been registered in Australia. It is an antiviral drug registered for use in eye treatment in some other countries (as 'Viroptic'). Trifluridine has also been called trifluorothymidine.

Trifluridine has 3 chiral centres; the drug substance is enantiomerically pure. Trifluridine is a white crystalline powder that melts at 180°C. It is soluble in water (60 mg/mL over the pH range 1 to 7.5). 2 polymorphic forms are known, designated Forms I and II. Form I is the one used in the proposed product.

Trifluridine is in class III of the Biopharmaceutics Classification System (BCS) (high solubility /low permeability), as shown in Figure 1.

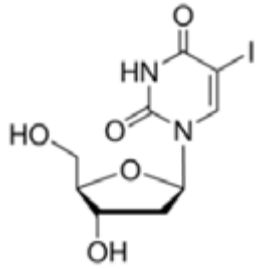
Figure 1: Trifluridine structure



trifluridine
'FTD'
$C_{10}H_{11}F_3N_2O_5$
MW 296.2

The related idoxuridine is registered in Virasolve cream (iNova) for use in the treatment of cold sores (Figure 2).

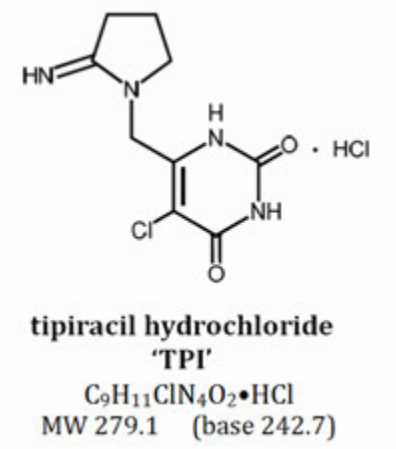
Figure 2: Idoxuridine structure



Tipiracil hydrochloride

Tipiracil hydrochloride (Figure 3) is a white crystalline powder that melts at 240°C. It is freely soluble (120 mg/mL) over the pH range 1 to 7.5 in aqueous media. At least 3 polymorphic forms are known. Form I is used in the proposed product.

Figure 3: Tipiracil hydrochloride structure



tipiracil hydrochloride
'TPI'
$C_9H_{11}ClN_4O_2 \bullet HCl$
MW 279.1 (base 242.7)

Tipiracil hydrochloride is in Class III of the BCS classification scheme (high solubility/low permeability). Tipiracil increases plasma trifluridine concentrations by inhibiting thymidine phosphorylase. Tipiracil is not the subject of official monographs. Impurity levels are low (individually all below 0.10%).

Particle size is controlled during tablet manufacture as it affects the assay uniformity between tablets; it does not significantly affect dissolution.

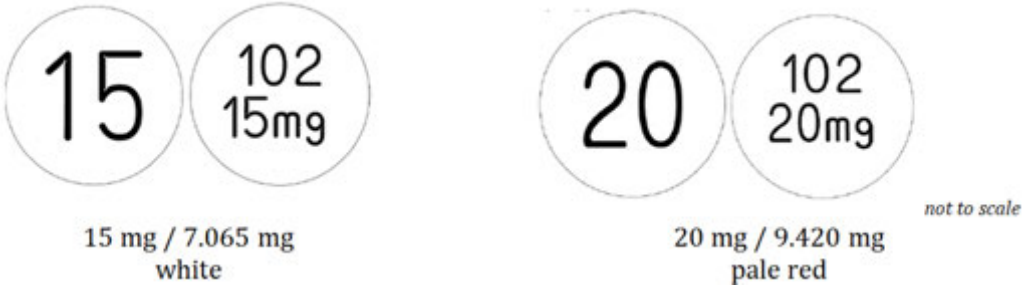
The tablets are formulated with tipiracil hydrochloride, but labelled with the equivalent quantity of tipiracil as is now usual.

Drug product

Recommended dosing is in a 28 day cycle and based on body surface area (BSA), with starting doses of 35 mg/m^2 twice daily, rounded to the nearest 5 mg increment (dosing details address trifluridine only). Dosing is adjusted based on adverse events. A maximum dose of 80 mg is recommended.

The 2 strengths are round, film coated, unscored tablets. They are slightly distinguished by size (7.1 and 7.6 mm) but also by markings and colour. The markings stress the trifluridine contents (15 or 20 mg), albeit with a slightly confusing '102' printing (Figure 4).

Figure 4: Markings on tablets



Bioavailability

The pharmacokinetic (PK) characterisation of new chemical entities should establish their systemic availability. The absolute bioavailabilities of trifluridine and tipiracil have not been determined, even though solution formulation should be straightforward. Reasons have not been given. Studies with oral radiolabelled doses suggest significant absorption of trifluridine and moderate absorption of tipiracil hydrochloride. Single dose administration of the combination dramatically increases trifluridine exposure.

Clinical trial formulations

Clinical studies used either the 'Early CTM Formulation' or 'Late Clinical Trial Material Formulation' tablets. These are identical except for film coat details and tablet shape. They are identical to the formulations proposed for registration except for printing details. In vitro dissolution of both formulations is complete within 15 minutes. Given the similarities, a bioequivalence comparison is not required.

Relative bioavailability

Study TPU-TAS-102-104 was a crossover bioequivalence study comparing 'Late Clinical Trial Material Formulation tablets' (3 x 30 mg tablets) and an oral solution (60 mg FTD/40 mL; drugs and water only) in patients. The relative bioavailability of the tablets compared to an oral solution was 100% (FTD) and 96% (TPI). Mean plasma peak concentrations were slightly higher for both drugs after solution dosing. The 90% confidence interval for trifluridine peak concentrations (C_{max}: 0.79 to 0.95) were just outside standard bioavailability limits (0.8 to 1.25). Overall, the results are consistent with the tablets being nearly 'optimally formulated'.

Food effect

Study J004-10040040 was the only study of the effect of food effect on pharmacokinetics. 14 evaluable patients received single 35 mg/m^2 doses after fasting or with a high fat meal. Food markedly reduces peak plasma exposure for both drugs. Trifluridine exposure (AUC_{inf}) with food is only slightly reduced within bioequivalence limits (96%; 90% CI 0.86 to 1.07), even though tipiracil exposure is markedly reduced (56%; 90% CI 0.49 to 0.64). The sponsor notes a correlation between trifluridine C_{max} and decreases in neutrophil count in one study, so recommends taking the tablets with food (which lowers C_{max}). The PI recommends taking tablets with a glass of water within one hour after completion of the morning and evening meals.

Quality summary and conclusions

Good Manufacturing Practice (GMP) clearances and labelling details are currently being finalised. Registration is otherwise recommended with respect to chemistry, quality control and biopharmaceutic aspects.

IV. Nonclinical findings

Introduction

The submitted dossier was compliant with the relevant International Conference on Harmonisation (ICH) guideline on the development of anti-cancer pharmaceuticals. All pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions. In this report, the dose refers to FTD dose of the FTD:TDI combination or FTD alone unless indicated otherwise. The TPI dose of the FTD:TDI combination is half the FTD dose on a molar basis.

Pharmacology

Primary pharmacology

FTD:TDI has been developed to treat refractory colorectal cancer. Following uptake into cancer cells, FTD, is phosphorylated by thymidine kinase (TK), further metabolised in cells to a DNA substrate, and incorporated directly into DNA, where it interferes with the DNA function to prevent cell proliferation. FTD can be rapidly degraded by thymidine phosphorylase (TPase) and readily metabolised by a first-pass effect following oral administration, and therefore tipiracil, a thymidine phosphorylase inhibitor (TPI) is included in this drug.

Anti-tumour efficacy of FTD occurs through its incorporation into DNA to disrupt DNA synthesis. To test FTD uptake into cellular DNA, NUGC-3 human gastric cells and MCF-7 human breast cancer cells were incubated with FTD for 4 and 24 h with FTD. The results showed FTD uptake was less than that of thymidine, but greater than that of other nucleoside analogues tested, including 1-beta-Darabinofuranosylcytosine (Ara-C), gemcitabine (dFdC), and 5-fluoro-2'-deoxyuridine (FdUrd). This suggests that FTD is readily taken up by DNA where it is likely to disrupt its function and exert its anti-tumour activity.

In vitro studies showed that, FTD inhibited the proliferation of various human cancer cell lines with half maximal inhibitory concentration (IC50) values of 0.214 μM to 24.4 μM and this activity were similar to the registered anti-cancer agent, 5-fluorouracil (5-FU) which

had IC50 values of 3.18 to 14 μM. FTD was 2 fold less potent than 5-FU in inhibiting proliferation of HCT-15 human colorectal cancer cells (IC50 value 10.7 μM and 4.96 μM, respectively, compared with the clinical free fraction C_{max} of around 0.5 μM).

In vivo, a series of studies were undertaken in nude mice, bearing a variety of human tumour xenografts, to establish the anti-tumour efficacy of FTD:TDI. FTD:TDI showed anti-tumour activity in various human colorectal cancer xenograft models in nude mice, which included KRAS wild-type (COL-1 cell line), cetuximab-resistant KRAS mutant (HCT-116 cell line) xenografts, inhibiting subcutaneous tumour growth by around 66% at 75 mg/kg PO BD (compared with cetuximab not effective against HCT-116 but inhibited COL-1 by 81%). At the same dose, FTD:TDI prolonged survival of mice intraperitoneally implanted with colon adenocarcinoma cells (KM20C) by 87%, and inhibited tumour growth by only around 25% in the subcutaneous xenograft model of KM20C at the same dose. Based on results of a mouse pharmacokinetic study (FTD C_{max} 33.8 μg/mL, $AUC_{0\text{-}24h}$ 22.9 μg.h/mL at 62.5 mg/kg), exposures in the mouse xenograft models at 75 mg/kg BD were 45 x and 7 x the clinical exposures at the clinical dose of 35 mg/m^2 based on free fraction C_{max} and AUC, respectively (clinical C_{max} 5.4 μg/mL, $AUC_{0\text{-}12h}$ 24.5 μg/mL; free fraction 3% in human plasma, 18% in mouse plasma). FTD:TDI also demonstrated anti-tumour activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines transplanted in nude mice. Anti-tumour effect of FTD:TDI at a dose level of 150 mg/kg was significantly higher than 5-FU and UFT against 5-FU-resistant tumours (70% inhibition rate (IR) was observed when treated with FTD:TDI, 38% IR with IV 5-FU, 28% with continuous infusion (CI) 5-FU and 12.9% with UFT treatment). Effects of 150 mg/kg FTD:TDI against 5-FU sensitive tumours were comparable to the effects of 5-FU and UFT (53% IR was observed when treated with FTD:TDI, 52% IR with IV 5-FU and 51% with UFT treatment).

FTD:TDI was also effective against human breast cancer xenografts in mice. Oral route at 25 mg/kg BD was shown to be more effective in inhibiting tumour growth when compared to continuous IV infusion at 2 mg/kg/day (59.4% compared with 26.2%). FTD:TDI given as a divided dose was shown to be superior in tumour growth inhibition to once daily dosing (76.5% at 75 mg/kg BD in contrast to 48.2% at 150 mg/kg). A high degree of association (R2 = 0.84) between the anti-tumour efficacy of FTD and the amount of FTD incorporated into DNA was established in various tumour models, confirming the proposed mechanism of action of this drug where FTD interacts with DNA and disrupts its function, exerting its anti-tumour activity.

TPI was shown to be a competitive inhibitor of recombinant human TPase (Ki 17 nM). It did not inhibit uridine phosphorylase, thymidine kinase, orotate phosphoribosyltransferase or dihydropyrimidine dehydrogenase.[4] TPI alone did not show any anti-tumour activity in mouse xenograft models; however, TPI at equimolar doses increased FTD exposures by around 2 fold in mice and around 100 fold in monkeys compared to animals administered FTD alone. Inhibition of FTD metabolism to 5-trifluoromethyl-2,4 (1H,3H)-pyrimidinedione (FTY) was also demonstrated in rats by higher urinary excretion of FTD and lower FTY exposure with the FTD:TDI combination than that with FTD alone. The species difference in the effect of TPI on FTD exposure was probably due to the difference in tissue distribution of TPase. TPI inhibited the degradation of FTD in extracts from liver of human, rodents and monkey, small intestine of human and monkey, and human tumour, but not in rodent and dog intestine or dog liver. In a monkey pharmacokinetic study, FTD was rapidly metabolised to its metabolite FTY following oral administration (bioavailability 3%), but co-administration of TPI with FTD (molar ratio 1:0.5) enhanced oral bioavailability of FTD around 112 fold. These studies support the conclusion that the major role of TPI in FTD:TDI is to enhance the exposure of

[4] Fukushima M, et al. Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2'-deoxyribonucleosides. *Biochem Pharmacol* 59: 1227-1236 (2000).

FTD. FTD and TPI at a molar ratio of 1:0.5 was determined to be the optimal molar ratio of FTD:TDI for clinical use based on a monkey study (FTD AUC values 1.01, 1.40 and 1.69 mg.min/mL at FTD:TDI molar ratios of 1:0.2, 1:0.5 and 1:1, respectively).

The sponsor did not determine the pharmacological activity of the FTD metabolite, FTY. Published studies showed that FTY did not exert significant growth inhibitory activity against Hela tumour cells (IC90 of FTY > 10 μg.ml compared with FTD 0.07 μg.ml).[5] In transplanted tumours (sarcoma, adenocarcinoma, Ehrlich ascites carcinoma and L1210 leukaemia) in mice, only a small effect was seen against Ehrlich ascites carcinoma by FTY compared to marked activity against all 4 tumours by FTD.[6]

In pharmacodynamic drug interaction studies, in vitro interactions between FTD and thymidine analog-type antiviral drugs in HCT-116 and NUGC-3 human gastric cells were assessed. Treatment with >10 μM zidovudine (AZT) enhanced FTD induced inhibition of NUGC-3 and HCT-116 cells following 4 and 72 h incubation.

Secondary and safety pharmacology

No secondary pharmacology studies were conducted except for one published study investigating enzyme inhibitory activities of TPI (discussed above). Specialised safety pharmacology studies covered the cardiovascular, respiratory and CNS systems. Single oral administration of FTD:TDI up to 435 mg/kg, FTD alone up to 435 mg/kg or TPI alone up to 2000 mg/kg had no significant effect on respiratory and CNS systems up to 24 hours post-dose in male rats (animal to human exposure ratio: around 30 for FTD and around 75 for TPI based on free fraction C_{max} obtained from toxicity studies; free fraction 28% in rat plasma).

Neither FTD (3 to 300 μM) nor TPI (1 to 100 μM) influenced in vitro hERG mediated potassium currents in stably transfected HEK293 cells, indicating low potential to cause QTc[7] prolongation. Similarly, single oral administration of FTD:TDI at up to 108.8 mg/kg, FTD alone at up to 108.8 mg/kg or TPI alone at up to 1000 mg/kg showed no significant treatment related effect on any cardiovascular parameters in monkeys (relative exposure: around 10 for FTD and around 60 for TPI based on free fraction C_{max}; free fraction 9% in monkey plasma).

The proposed clinical dose is not expected to affect CNS, respiratory and cardiovascular functions.

Pharmacokinetics

Absorption

Both components of FTD:TDI were rapidly absorbed from the GI tract following oral administration in mouse, rats and monkeys (tmax 0.25 to 1 h in mice and rats, 0.5 to 3 h in monkeys). Greater absorption of radioactivity derived from FTD compared with that derived from TPI was seen in pharmacokinetic studies in rats and monkeys dosed with the

[5] Takeda S, et al., Antitumor activity of FTC-092, a masked 5-trifluoromethyl-2'- deoxyuridine deriviative. *Cancer Chemother Pharmacol.* 29: 122-6 (1991).
[6] Heidelberger C, Anderson SW. Fluorpyrimidines. XXI. The tumor inhibitory activity of 5-trifluoromethyl-2'-deoxyuridine. *Cancer Res.* 24: 1979-85 (1964).
[7] The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

combination (one component was radiolabelled). The oral bioavailability of FTD and TPI was 31% and 9%, respectively, in rats, and the half-life was 2 and 2.6 h after an oral dose. A study using an in situ loop method in rats revealed that FTD was absorbed in the entire gastrointestinal tract; however, absorption was highest in the middle and distal small intestine and lowest in the stomach. TPI was absorbed primarily in the small intestine, with only low levels of absorption by the stomach and large intestine. In pharmacokinetic and toxicokinetic analyses in animals, exposure to FTD and TPI increased with increasing dose level over the dose ranges studied and were dose proportional. There was no notable change in exposure upon repeated dosing, indicating that accumulation was not evident, nor was there any notable sex differences in exposure in all the animal species tested.

Distribution

FTD was highly bound to plasma protein (primarily to albumin) from humans (around 97%) and monkeys (around 91%), and binding was lower in mice (around 82%), rats (around 72%) and dogs (around 45%). FTD did not displace the albumin-bound drug warfarin in human plasma, and nor was the extent of FTD binding affected by the presence of other albumin bound drugs (diazepam or digitoxin). TPI plasma protein binding was very low in human and all other species studied (< 10% in all species). Drug related material was associated mainly with plasma, with very low distribution to blood cells for both FTD and TPI (blood/plasma ratio of FTD and TPI of 0.6 to 0.8 in rat, monkey and human blood in vitro; around 20% distribution to blood cells in rats in vivo).

Distribution in vivo in rats after oral dosing with FTD:TDI (radiolabelled FTD or TPI) showed that radioactivity was associated mainly with organs of absorption and excretion (which included kidney, ileum, urinary bladder, stomach and jejunum). Radioactivity levels in non-absorption/excretion organs were below the plasma level. There was some distribution of FTD:TDI in the brain (3 to 7% of that in plasma at 1 h post dose) and also to testes (29% of plasma level at 1 h. Tissue radioactivity declined along with plasma levels. No preferential binding of drug related material to the melanin containing tissues were observed.

Metabolism

FTD is predominantly metabolised to FTY by TPase, which is inhibited by TPI in vitro and in vivo in rats, monkeys and humans following oral administration. High exposures to FTY occurred in animals for assessing potential metabolite-mediated toxicity. Additional minor metabolites of FTD, that is, 5-carboxyuracil (5-CU) and 5-carboxy-2'-deoxyuridine (5-CdUrd) accounted for ≤ 8% and ≤ 2% in human hepatocytes. Addition of TPI changed these percentages to ≤ 2.2% and ≤ 3.1% respectively. 5-CdUrd was formed non-enzymatically. These metabolites were not detected in rat or monkey plasma, urine or faeces in the sponsor's pharmacokinetic studies, but 5-CU and 5-CdUrd were reported to be detected in monkey urine, and 5-CU in mouse urine after an IV dose of FTD. One metabolite (named as HFP1, ≤ 8% of total drug-related components) detected in rat plasma and one (named as HFU1, ≤21% (7% of dose), unaffected by TPI) in rat urine were not identified. Given only trace amounts of 5-CU and 5-CdUrd were detected in human plasma, and the advanced cancer indication, further metabolite evaluation is not required. In vitro metabolism results using human hepatocytes were consistent with the metabolism of FTD seen in humans in vivo. No FTD or TPI metabolites were detected in human liver microsomes in vitro, suggesting that FTD and TPI are not metabolised by CYP450. TPI was largely non-metabolised, with a minor biotransformation product (6-HMU) detected in humans (that is, only when higher doses of FTD:TDI (50 to 70 mg/m^2/day were administered), while 6-HMU is a major metabolite in rats (around 3.5% of dose in urine and 13% of dose in faeces). No other metabolites of TPI were detected. The metabolism of TPI was unaffected by FTD in rats.

Excretion

FTD and TPI are rapidly eliminated in rats and monkeys with elimination half-life of < 3 h for both ingredients. Excretion of orally absorbed drug-related material was predominantly via urine for FTD (around 60% of dose in rats, around 80% in monkeys, compared with 55% in human urine). Faecal excretion (around 20% of FTD dose in rats, around 4% in monkeys) and excretion in expired air (around 16% of dose in rats) were also observed. TPI was predominantly excreted in faeces (around 84% of the dose in rats, 68% in monkeys), with urinary excretion accounting for around 15% of the dose in rats and around 27% in monkeys (compared with 27% in urine and 50% in faeces of humans). FTY and unchanged TPI were the predominant components in rat and monkey urine or faeces. As expected the excretion of unchanged FTD was higher in animals dosed with FTD:TDI than that with FTD alone.

Conclusion

FTD:TDI showed similar absorption, distribution and metabolism in rats, monkeys and humans, although protein binding of FTD differs between animal species and humans. The animal species are suitable for assessing the potential toxicity of FTD:TDI in humans.

Pharmacokinetic drug interactions

FTD and TPI are not metabolised by cytochrome P450. In vitro studies have shown that FTD, TPI and FTY did not inhibit CYP isoforms (isoforms tested: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). In vitro FTD, TPI and FTY had no inductive effect on human CYP1A2, CYP2B6 and CYP3A4 activity or mRNA levels. These results suggest that FTD, TPI and FTY are neither inducers nor inhibitors of CYP and therefore, are unlikely to cause or be affected by a CYP mediated drug interaction.

In vitro evaluation of FTD and TPI was conducted using a range of human uptake and efflux transporters (FTD was tested with MDR1/P-gp, OATP1B1, OATP1B3, CNT1, ENT1, ENT2 and BCRP; TPI was tested with OAT1, OAT3, OCT1, OCT2, OCT3, OCTN2, MATE1, MDR1/P-gp and BCRP). FTD and TPI were neither an inhibitor of nor a substrate for majority of these transporters however there were a few exceptions. TPI was found to be a substrate and inhibitor of OCT2 and MATE1 (both are major transporters for the secretion of drugs into the urine). Since TPI is mainly excreted in faeces, effects of OCT2 and MATE1 inhibitors on plasma TPI concentrations in patients are expected to be low. The IC50 value of TPI against OCT2 was 0.946 mM (equivalent to 230 µg/mL) and IC50 value of TPI against MATE1 was 0.092 mM (equivalent to 25.7 µg/mL) which is substantially higher (> 3000 times or 300 times respectively) than the clinical C_{max} of 0.079 µg/mL (after repeated dosing of FTD:TDI at 35 mg/m^2 twice daily and therefore is unlikely to inhibit the transporter in patients. Since TPI is a substrate of OCT2 and MATE1, the plasma TPI concentration is likely to increase when FTD:TDI is administered concomitantly with inhibitors of OCT2 and MATE1. FTD is a substrate for nucleoside transporters CNT1 (Study 14DB11), ENT1 and ENT2.[8] Therefore caution is required when using medicinal products that interact with these transporters.

[8] Sakomoto K, et al. Crucial roles of thymidine kinase 1 and deoxyUTPase in incorporating the antineoplastic nucleosides trifluridine and 2'-deoxy-5-fluorouridine into DNA. *International Journal of Oncology* 46: 2327-2334 (2015).

Toxicology[9,10]

Acute toxicity

The single dose oral toxicity of FTD:TDI and the individual components, FTD and TPI, was investigated in rats, and FTD:TDI and FTD in dogs. The acute toxicity of FTD:TDI and FTD alone were found to be similar in both species. The approximate non-lethal dose of FTD in rats was 1000 mg/kg for FTD:TDI or FTD alone. The non-lethal dose of FTD in dogs was 1000 mg/kg in males and 2000 mg/kg in females for FTD:TDI and 2000 mg/kg in both sexes for FTD alone. The gastrointestinal tract was identified as the primary target organ in both species. Diarrhoea, vomiting, abnormal stools, decreased food consumption and reduced bodyweight were observed in both species dosed with FTD:TDI or FTD alone and at necropsy, and changes in the gastrointestinal tracts were also observed.

TPI alone was well tolerated in rats and had a maximum non-lethal dose of >2000 mg/kg. The high dose of 2000 mg/kg had no significant toxicological effect (only salivation and white coloured stool were observed). No TPI related effects were observed in the gastrointestinal tract.

Repeat dose toxicity

GLP compliant studies examined the toxicity of repeat doses of FTD:TDI (7 studies), FTD alone (5 studies plus a non GLP compliant study) in rats, dogs and monkeys and TPI alone (3 studies) in rats and monkeys. 2 main studies of FTD:TDI for 13 weeks duration were conducted in both rats and monkeys, with each study including a recovery period of 9 weeks. FTD:TDI was administered orally by daily gavage, consistent with the route of administration in humans. Group sizes, and study duration were adequate. The studies conducted were consistent with ICH Guideline S9 (anticancer pharmaceuticals) and the EU Guideline on repeated dose toxicity.

Relative exposure

The dosage regimen in the animal studies does not fully replicate the clinical situation. Dosing in all studies was only once daily, whereas dosing clinically is intended to be twice daily on Days 1 to 5 and Days 8 to 12 per dosing cycle. Exposures achieved were much lower and in most cases plasma FTD were cleared by the animals within 4 to 8 h post dose. Pivotal study dosing was selected based on toxicity findings in preliminary 14 and 28 day studies in both rats and monkeys. Higher doses that would be more clinically relevant were not achievable due to the toxicity of FTD in these animals. Due to the low exposures achieved in the pivotal 13 week studies, the majority of the findings described below should be assumed to be potentially clinically relevant.

Exposure ratios have been calculated based on weekly exposures in animal studies and in patients, and for FTD based on free fraction plasma concentrations due to large

[9] Careful consideration of the doses used in nonclinical studies is necessary to fulfil the scientific needs of safety assessment and to satisfy regulatory authorities. The current Committee for Proprietary Medicinal Products (CPMP) note for guidance on repeated dose toxicity studies indicates that doses should be selected to establish a dose or exposure response to treatment. This can generally be achieved by the use of 3 groups of animals receiving the test item, at low, intermediate and high doses, plus a control group which receives vehicle alone. Experience has shown that 3 doses will usually cover the span between no effect and adverse effects although there are exceptions. The CPMP guidance also indicates that the high dose should be selected to enable identification of target organ toxicity, or other non-specific toxicity, or until limited by volume or limit dose. In addition to establishing toxicity, it is necessary from a scientific perspective to establish the No Observed Effect Level (NOEL) and/or the No Observed Adverse Effect Level (NOAEL) that may be used along with other information, such as the pharmacologically active dose, to determine the first dose in human studies.

[10] LD = low dose, MD = middle dose and HD = high dose used in a particular nonclinical study.

inter-species differences in protein binding. Low exposures were achieved in the pivotal 13 week studies in rats (exposure ratios up to 6 for FTD and 8 for TPI) and monkeys (exposure ratios up to 14 for FTD and 4 for TPI). Exposures to the main FTD metabolite, FTY in rats were high (exposure ratio up to 105). Blood samples were collected in the 4 week studies with the FTD:TDI combination only at 2 time points and no AUC values could be accurately estimated. Thus, exposures obtained in 2 week studies are included in the exposure table below. No significant difference in plasma drug levels was generally observed between male and female animals, and there was no increase in exposure after repeated dosing.

Table 2: Relative exposures in repeat-dose toxicity studies when dosed with FTD:TDI

Species	Study; Treatment duration	Dose FTD+TPI (mg/kg/day)	FTD		FTY		TPI	
			$AUC_{0-24\,h}$ (µg·h/mL)	RE#*	$AUC_{0-24\,h}$ (µg•h/mL)	RE#	$AUC_{0-24\,h}$ (µg•h/mL)	RE#
Rat (SD)	2 weeks	15 + 7	1575	0.4	15726	2.1	443	0.8
		50 + 24	6186	1.7	43686	6	1405	2.6
		150 + 71	18601	5	124753	17	3028	6
		450 + 212	62410	17	398401	54	9892	18
	2 weeks	15 + 0	552	0.2	13217	1.8	-	-
		50 + 0	2357	0.6	38007	5	-	-
		150 + 0	9112	2.4	146916	20	-	-
		450 + 0	22291ǂ	6	344348ǂ	47	-	-
	4 weeks	0 + 2000	-	-	-	-	25048	46
	13 weeks	5 + 2.4	517	0.1	4825	0.7	189	0.3
		15 + 7.1	2175	0.6	14250	1.9	458	0.8
		50 + 24	7165	1.9	33950	4.6	1230	2.2
		150 + 71	22400	6	771000	105	4340	8
Dog (Beagle)	2 weeks	17 + 8	11528	3.1	58783	8	3254	6
	2 weeks	2 + 0	532	0.1	-	-	-	-
		6 + 0	6620	1.8	-	-	-	-
		17 + 0	18731ǂ	5	-	-	-	-
Monkey (Cynomol -gus)	2 weeks	1.9 + 0.9	1229	0.3	1263	0.2	36.5	0.1
		7.5 + 3.5	16384	4.4	4999	0.7	317	0.6
		30 + 14	65801	18	18561	2.5	1286	2.4
		120 + 57	143603	38	98644	13	4483	8
	4 weeks	6.25 + 0	23.3	<0.1	8070	1.1	-	-
	4 weeks	25 + 0	263	<0.1	35273	4.8	-	-
		50 + 0	2407ǂ	0.6	137299ǂ	19	-	-
		100 + 0	4101ǂ	1.1	190349ǂ	26	-	-
		150 + 0	12349ǂ	3.3	262129ǂ	36	-	-
	4 weeks	0 + 100	-	-	-	-	9679	18
		0 + 300	-	-	-	-	16918	31
		0 + 1000	-	-	-	-	41175	75
	13 weeks	1.25 + 0.59	2435	0.6	1485	0.2	198.5	0.4
		5 + 2.36	14450	3.8	4465	0.6	594.5	1.1
		20 + 9.42	52850	14	18150	2.5	2155	3.9
		20 + 0	554	0.2	35450	4.8	-	-
Human	Day 12 (Cycle1)	35 mg/m^2 BD	49092$	-	10328$	-	766$	-

RE, relative exposure; # animal: human plasma AUC, normalised to weekly exposure (animal AUC x 7, human AUC x 5); Animal AUC after the last dose except for values marked with ǂ after the first dose; * based on FTD free fraction: 28% in rats, 55% in dogs, 9% in monkeys and 3% in humans; $ $AUC_{0\text{-}12h}$ x 2.

Major toxicities

The toxicities of FTD:TDI and FTD alone were found to be very similar, with no additional effects when FTD was administered in conjunction with TPI. The major target organs for FTD:TDI and FTD alone was the lymphohaematopoietic systems, the gastrointestinal tract and reproductive organs in rats and monkeys. These findings were partially or fully reversible in a period of 4 to 9 weeks.

Gastrointestinal effects in rats and monkeys included diarrhoea, decreased food intake, and decreased body weight. In the gastrointestinal tract, erosion, necrosis of glandular epithelial cells throughout the gastrointestinal tract and increase in apoptotic bodies were seen associated with gastrointestinal disturbances. Similar effects were also seen in dogs.

Lymphohaematopoietic findings in rats and monkeys included:

- dose dependent decreases in WBC count, RBC count, reticulocytes haemoglobin level and haematocrit;
- lymphoid atrophy of the thymus, spleen and lymph nodes;
- decreases in haematopoietic cells and myeloid: erythroid ratio of the bone marrow; and
- fatty infiltration of bone marrow.

A compensatory increase in extramedullary haematopoiesis of spleen was seen in rats. Lymphohaematopoietic systems were also affected in dogs.

Reproductive organ abnormalities were observed in rats and monkeys dosed with the FTD:TDI combination or FTD alone. In rats, findings included increased number of small corpus lutea, and increased ovary weights at ≥ 150 mg/kg/day in the 4 week study with FTD:TDI, and atrophy of seminiferous tubules in the testis, decreased sperm and increased cellular debris in the tubules of the epididymis at 450 mg/kg/day FTD:TDI or FTD for 2 to 4 weeks. In monkeys, seminiferous tubule epithelial degeneration and necrosis and multinucleated giant cell formation in the testes were seen at lethal doses (≥ 100 mg/kg/day), and immature testes, uterus and vagina atrophy at the highest dose in the 13 week study.

Abnormalities of incisors, such as whitening, breakage and malocclusion were observed in rats at ≥ 50 mg/kg/day. Histological examination showed disarrangement of the ameloblasts, odontoblasts and osteodentin. These effects were reversible after a 9 week withdrawal in the 13 week study. These abnormalities were considered to be specific to rodents (not seen in monkeys) due to their persistently growing teeth and it's unlikely to be clinically relevant in an adult human population, but may occur in paediatric patients.

TPI was not toxic in rats at up to 2000 mg/kg/day. The only TPI related findings were visible urinary or faecal excretion of test material at high doses (cloudy urine, spherical crystals in urine and white faeces). In monkeys, gastro-intestinal tract inflammation/mucosal hyperplasia, lymphoid atrophy, and liquid faeces were observed at ≥ 300 mg/kg/day TPI alone, with no effects at 100 mg/kg/day.

Genotoxicity

The genotoxic potential of FTD:TDI, as well as that of FTD alone and TPI alone were tested in bacterial reverse mutation assays, in vitro chromosome aberration assays, in Chinese hamster ovary cells and in vivo micronucleus tests. This testing strategy was consistent with ICH Guideline S2 (R1): Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. These studies showed both FTD:TDI and FTD exhibited the potential to induce reverse mutation, chromosomal aberration and micronuclei. TPI showed no genotoxicity when tested at high concentrations of ≥ 2000 mg/kg. Genotoxicity is identified as a risk in patients.

Carcinogenicity

No carcinogenicity studies were submitted which is acceptable for an anticancer pharmaceutical treatment of advanced cancer (ICH Guideline S9: Nonclinical Evaluation for Anticancer Pharmaceuticals). Given the positive findings in all genotoxicity assays conducted with FTD:TDI and FTD alone, FTD is expected to be carcinogenic.

Reproductive toxicity

2 GLP fertility and early embryonic development and 2 embryofetal development studies (one non-GLP pilot study and one pivotal study) were conducted. No toxicokinetic data were obtained from any of these 4 reproduction studies. Effects on male and female fertility were separately assessed in rats. Embryofetal development studies in rats showed clear evidence of embryofetal lethality, and a confirmatory study in rabbits was not conducted. Pre-/postnatal development studies were not performed. The reproductive toxicology program is acceptable according to the ICH Guideline S9.

Placental transfer and excretion into milk of FTD:TDI was detected in rats dosed with radiolabelled 14C-FTD or 14C-TPI. Radioactivity was detected in fetuses after oral administration of FTD:TDI (14C-FTD or 14C-TPI) to pregnant rats. Both FTD and TPI were able to cross the placenta and FTD crosses at a higher rate than TPI (fetal/maternal blood radioactivity ratio at 0.5 to 1 h: 0.3 to 0.4 for FTD and 0.12 for TPI). Radioactivity was also excreted in the milk of nursing rats dosed with FTD:TDI (14C-FTD or 14C-TPI), with milk/plasma ratio at 1 to 2 h: 0.47 to 0.61 for FTD and 0.35 to 1.29 for TPI.

In the male fertility study, administration of FTD:TDI to males at doses up to 450 mg/kg for 14 days prior to and during mating with untreated females did not have effects on male fertility and early embryonic development. Based on toxicokinetic data in the 2 week repeat dose study in rats the FTD relative exposure at the highest dose was 17 x the human exposure at 35 mg/m^2 BD It is worth noting that repeat dose toxicity studies with the same dose of FTD showed mild atrophy of the seminiferous tubules in the testis and decreased sperm counts (discussed above under 'Repeat dose toxicity').

Similarly, administration of FTD:TDI up to 150 mg/kg/day (around 5 x the human exposure), daily for 14 days to female rats before mating with untreated males and during mating and the first 7 days of gestation did not affect female fertility, but the number of viable embryos was decreased at 150 mg/kg/day, suggesting an effect on early embryonic development (no effect at 50 mg/kg/day, similar to human exposure). Other findings in the female fertility study were increases in the number of corpora lutea and implantations at 150 mg/kg/day. Increased number of corpora lutea was also observed in the 4 week repeat dose study with FTD:TDI.

When FTD:TPI was administered to female rats during organogenesis, increased embryofetal lethality (post-implantation loss), delayed ossification, as well as external anomalies (kinked tail, ectrodactyly, cleft palate and anasarca), visceral (great vessel anomalies (interrupted aortic arch, malpositioned subclavian branch, retroesophageal subclavian, left umbilical artery), membranous ventricular septal defect, malpositioned thymus (persistence in the neck), supernumerary lung lobe, convoluted ureter, dilated ureter) and skeletal abnormalities (including incomplete/extra ossification of multiple bones, full or short supernumerary ribs, fused vertebrae, supernumerary thoracic vertebrae, misaligned sternebrae, sternoschisis) were observed at 150 mg/kg/day. The incidences of full or short supernumerary ribs, supernumerary thoracic vertebrae and unossified phalanges were also increased at 50 mg/kg/day. Fetal weight was decreased at doses ≥ 50 mg/kg. The only maternal effect was decreased food consumption and body weight gain at 150 mg/kg/day. Complete embryofetal loss occurred at higher doses (≥ 300 mg/kg/day) in a preliminary study.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[11] The severity of findings in the animal studies indicates this classification is appropriate. Teratogenicity was evident in rats at doses lower than the human dose and therefore Category D is appropriate.

Phototoxicity

The potential of FTD and TPI to induce phototoxicity in cultured mammalian cells was assessed using Balb/3T3 clone A31 cells derived from the mouse embryo. FTD and TPI concentrations tested ranged from 7.81 to 1000 μg/mL (based on results from preliminary studies) under non-irradiation and irradiation conditions. Neither FTD nor TPI inhibited cell growth by 50% or more at any of the concentrations tested in any treatment conditions. These results suggest that FTD and TPI are not phototoxic.

Nonclinical summary and conclusions

Summary

- The submitted dossier was compliant with the relevant ICH guideline on the development of anti-cancer pharmaceuticals. All pivotal toxicity studies were conducted under GLP conditions.
- Consistent with its activity as a thymidine analog, FTD was incorporated into the DNA of human cancer cells in vitro and quantification assays demonstrated correlation between uptake of FTD and anti-tumour efficacy. Incubation with FTD resulted in transient depletion of the intracellular pool of TTP, consistent with its ability to non-covalently bind and inhibit thymidylate synthase. In vitro, the anti-proliferation activity and selectivity of FTD against specific tumour cell lines was demonstrated with IC50 values ranging from 0.214 to 24.4 μM. In vivo FTD:TDI exhibited anti-tumour activity in various human colorectal cancer xenograft models in mice, including capacity to inhibit cetuximab resistant KRAS mutant xenografts (55.5% tumour growth inhibition) that are resistant to current therapy. FTD:TDI also demonstrated anti-tumour activity against both 5-FU sensitive and resistant colorectal cancer cell lines. The FTD metabolite, 5 FTY is not pharmacologically active.
- TPI inhibits the activity of thymidine phosphorylase. In vivo assays showed that TPI alone had no effect on tumour growth whereas FTD:TDI had anti-tumour activity.
- Safety pharmacology studies assessed effects of FTD:TDI, FTD alone and TPI alone on body temperature and respiratory parameters in the rat, as well as cardiovascular (electrocardiograph (ECG)) and blood pressure measurements in telemetered, conscious monkeys and in an in vitro hERG assay. No adverse effects were seen in male rats (at relative exposures of around 30 for FTD and around 75 for TPI based on free fraction or total C_{max}, respectively) or in monkeys (at relative exposures of around 10 for FTD and around 60 for TPI based on free fraction C_{max}) or with investigation of the hERG current in vitro.
- The pharmacokinetic profile in animals was qualitatively similar to that of humans. FTD:TDI was readily and rapidly absorbed with a similar T_{max} in all species. Plasma protein binding of FTD was high in humans and monkeys but lower in mice, rats and dogs; in contrast TPI plasma protein binding was very low in all species. Tissue distribution of FTD:TDI was wide but penetration into brain was limited. FTD:TDI was

[11] Australian Pregnancy Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

able to penetrate through the placenta and was detected in fetuses and milk of rats. The main human metabolite FTY was a significant metabolite in animals. Drug related material was excreted via urine and faeces with urine as the predominant route of excretion for FTD and faeces as the main route of excretion for TPI in humans and animal species.

- Based on in vitro studies, FTD:TPI is not expected to alter the exposure of co-administered drugs that are CYP450 substrates as it has neither an inhibitory or an inducing effect. TPI was found to be a substrate and inhibitor of OCT2 (a renal tubule uptake transporter) and MATE1 (multidrug and toxin extrusion protein) in vitro but the effect of OCT2 inhibitors on TPI elimination is expected to be small since TPI is mainly eliminated by faecal excretion. IC50 values of TPI against OCT2 and MATE1 were > 300 times the clinical C_{max} and therefore it is unlikely to inhibit these transporters in patients; however, plasma TPI levels may increase when FTD:TPI is administered concomitantly with inhibitors of these transporters. FTD is also a substrate for nucleoside transporters (CNTI, ENT1 and ENT2) and therefore caution is required when using medicinal products that interact with these transporters.
- Single dose toxicity studies in rats and dogs indicated a moderate to low order of acute toxicity.
- The main repeat dose studies by the oral route were conducted in rats and monkeys for 13 weeks with a 9 week recovery period. Due to the toxicity of FTD:TPI in these animals, the maximum exposures achieved were low in both animals (up to 6 and 8 for FTD and TPI in rats and 14 and 4 for FTD and TPI in monkeys). The major target organs were the gastrointestinal tract (necrosis of glandular epithelial cells and increase in apoptotic bodies associated with gastrointestinal disturbances), haematopoietic system (leukopaenia, anaemia and decrease in haematopoietic cells of the bone marrow) and lymphoid tissues (atrophy of the thymus, spleen, and lymph nodes). These effects were generally reversible in a period of 4 to 9 weeks. Bone marrow suppression, infection and gastrointestinal effects were identified as the main safety concerns. Abnormalities of incisors were observed in rats that may be applicable to paediatric population.
- FTD:TPI and FTD were positive in genetic toxicology tests (mutations, chromosomal aberrations and micronucleus) while TPI was negative. Therefore, FTD:TPI is mutagenic and clastogenic. No carcinogenicity studies were conducted, which is considered acceptable for anticancer drugs.
- GLP compliant reproductive toxicity studies examined male and female fertility and embryofetal development in rats. Fertility was unaffected in male rats treated with FTD:TPI before and during mating with untreated males at exposure levels 17 times the clinical AUC. Similarly, administration of FTD:TPI to female rats before mating with untreated males did not affect mating and pregnancy rates, but caused a decrease in viable embryos at exposures of 5 times the clinical dose suggesting an effect of FTD:TPI on early development. Increased post-implantation loss, decreased fetal weight, impaired ossification and increased skeletal, external and visceral variations and malformations were seen in embryofetal development studies in rats when dosed with 5 times the clinical AUC during organogenesis. Lower birth weight and skeletal variations (delayed ossification, supernumerary ribs/thoracic vertebrae) were observed at a lower dose (approximately 2 times the clinical exposure). As the studies in rats found clear evidence of embryofetal lethality a confirmatory study in rabbits was not required (ICH Guideline S9).
- Neither compound produced phototoxicity in cultured mammalian cells.

Conclusions and recommendation

- The primary pharmacology studies support the use of FTD:TPI for the proposed indication.
- No clinically relevant safety pharmacology hazards were identified based on stand-alone pharmacology studies in rats and monkeys.
- The main toxicities identified in repeat-dose studies were gastrointestinal, lymphatic and haematopoietic toxicity. Bone marrow suppression, infection and gastrointestinal effects were identified as safety concerns. Abnormalities of incisors observed in rats may also be applicable to the paediatric population.
- FTD:TPI is considered to pose a genotoxic and carcinogenic hazard.
- FTD:TPI is a teratogen and causes embryofetal lethality and malformations in rats. Pregnancy Category D is recommended as FTD is likely to cause human fetal malformations or irreversible damage.[11]
- Provided the above effects are adequately monitored or managed during clinical use, there are no objections on nonclinical ground to the proposed registration of Lonsurf.
- The draft PI should be amended as directed.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

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

The sponsor presented a new FDC containing a combination of FTD and TPI at a molar ratio 1:0.5 (weight ratio, 1:0.471) to be used in the treatment of mCRC. FTD is an antineoplastic thymidine-based nucleoside analog which is incorporated into DNA in tumour cells following phosphorylation. TPI inhibits degradation of FTD by inhibiting TPase, thus increasing systemic exposure to FTD when FTD and TPI are given together.

In Australia, patients with unresectable mCRC usually die from the disease, with 5 year overall survival of about 15%. The primary chemotherapy for mCRC is a combined regimen containing a fluoropyrimidine, such as 5-FU or capecitabine, along with other agents such as LV, irinotecan and oxaliplatin.

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

Guidance

There appear to have been no pre-submission meetings between the sponsor and the TGA. The sponsor warrants that the application is consistent with the pre-submission planning form.

Contents of the clinical dossier

The submission contained the following clinical information:

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

Paediatric data

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

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

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

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

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

- establish the tolerability of TAS-102 at a dose of 35 mg/m^2 BD in patients with solid tumours;

- demonstrate the effect of TPI on the PK of FTD;
- establish the relative bioavailability of TAS-102;
- investigate the effect of food on the PK of TAS-102;
- evaluate the QT corrected for heart rate (QTc) prolongation potential of TAS-102; and
- assess the intrinsic and extrinsic factors that might influence the PK of TAS-102 based on a population PK analysis.

Key PK clinical studies

The 6 key PK studies are briefly summarised below in Table 3.

Table 3: Key studies providing pharmacokinetic data

Study	Purpose	Population	N = (PK)	Dose
TPU-TAS-102-104. Phase I	Relative BA	US patients with advanced solid tumours (excluding breast) for which no standard therapy exists. Single dose PK data.	38	TAS-102 (15, 20 mg); 60 mg (3 x 20 mg tablets) and oral solution 60 mg/40 mL, single dose, crossover, 7 day washout, followed by OL extension.
J001-10040010. Phase I	PK/initial tolerability/dose finding	Japanese patients with confirmed solid tumours responding poorly to standard treatment. Single and repeat dose PK data.	21	TAS-102 tablets (15, 20 mg); escalating doses of 15 (n = 6), 20 (n = 3), 25 (n = 3), 30 (n = 3) and 35 (n = 6) mg/m^2 PO BD, proposed regimen.
J004-10040040. Phase I	Food effect	Japanese patients with solid tumours (excluding gastric cancer). Single dose PK data.	16	TAS-102 tablets (15, 20 mg); 2 doses of 35 mg/m^2 PO under fasting and fed conditions, crossover with ≥ 5 day washout, followed by OL extension.
TPU-TAS-102-101. Phase I	PK/initial tolerability/RP3D	US patients with refractory mCRC who had received ≥ 2 lines of prior chemotherapy for mCRC. No PK data.	27	TAS-102 tablets (15, 20 mg); 30 mg/m^2 (Cohort 1 (n = 3)) or 35 mg/m^2 (Cohort 2 (n = 9)) PO BD for 5 days a week with 2 days rest period for 2 weeks, followed by a 14 day rest period, repeated every 4 weeks (sequential cohorts plus expansion cohort (n = 25) at 35 mg/m^2); 28 day cycles continued until discontinuation criterion met.
TPU-TAS-102-102. Phase I	PK/initial tolerability	US patients with solid tumours (excluding breast cancer) for which no standard therapy exists. Single-dose PK data for FTD after TAS-102 and FTD alone.	39	PK (Part 1) data for FTD after TAS-102 and FTD alone after single-dose 35 mg/m^2, followed by OL extension (Part 2).

Study	Purpose	Population	N = (PK)	Dose
TPU-TAS-102-103 Phase I	Cardiac safety; PK/PD analysis	US patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists.	41	TAS-102 (15, 20 mg tablets); cardiac safety (Cycle 1) single blind PO placebo dose on Day -1, TAS-102 35 mg/m^2 PO BD on Days 1 to 5 and Days 8 to 12 with rest days 13-28, followed by OL extension.

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

Initial dose-finding legacy studies (5 studies)

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

Population PK study (Study 12DA25)

The submission included one population PK study (Study 12DA25), which pooled data for FTD and TPI obtained from dense sampling from 3 Phase I studies (Studies J001-10040010, TPU-TAS-102-102, and TPU-TAS-102-103) and from sparse sampling from the pivotal Phase III study (Study TPU-TAS-102-301; also known as RECOURSE).

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

Evaluator's conclusions on pharmacokinetics

- The submitted data are considered to have adequately characterised the PK of FTD and TPI when administered as a FDC tablet (TAS-102) at the proposed dose of 20 to 35 mg/m^2 BD (based on BSA) for the treatment of advanced mCRC. The PK data were based on studies in patients with advanced cancer (solid tumours). There were no PK data in healthy volunteers, but this is considered to be acceptable given that FTD is a cytotoxic agent. The PK results derived from non-compartmental analysis for the single dose and multiple dose studies contributing relevant PK data for FTD, TPI and relevant metabolites are summarised.
- The major limitations of the PK data relate to the absence of dedicated clinical studies assessing the effects of hepatic and renal impairment on the PK of TAS-102. However, the sponsor has indicated that such studies will be submitted to the EMA by the end of 2017.
- The submission included a number of human biomaterial studies investigating the in vitro effects of FTD and TPI on various enzyme systems relating to metabolism and potential drug-drug interactions. Data from these in vitro studies were presented in

the submission. It is recommended that definitive evaluation of this in vitro data be undertaken by the nonclinical evaluator.

- 2 tablet formulations were used in the clinical studies (Early CTM and Late CTM formulations), and the TBM tablet formulation is stated by the sponsor to be identical to the Late CTM tablet formulation with the exception of ink imprinting. There were no clinical bioequivalence studies comparing the 3 formulations. However, in vitro dissolution data are reported to show similarity between the Early and Late CTM formulations. Based on the in vitro dissolution data the sponsor predicts that the in vivo performance of the Early and Late CTM formulations will be similar. In addition, the formulation similarities of the Late CTM and TBM formulations suggest that the in vivo performance of these 2 tablet formulations will also be similar. Overall, the in vitro data are considered to support the sponsor's decision not to submit dedicated clinical bioequivalence studies comparing the 3 tablet formulations. However, the definitive opinion about this matter rests with the pharmaceutical chemistry evaluator.
- Based on the submitted data relating to solubility and permeability of FTD and TPI, the 2 products are reported to be BSC Class III compounds (that is low permeability, high solubility). Following oral administration, both FTD and TPI are rapidly absorbed with mean T_{max} values of 1 to 2 hours for FTD and 2 to 3.5 hours for TPI. No absolute bioavailability study was submitted. The sponsor provided a justification for not submitting an absolute bioavailability study. The justification has been examined and is considered to be satisfactory. Based on urinary and faecal radiolabelled excretion data from the mass balance study it can be estimated that following an oral dose of TAS-102 absorption of FTD is ≥ 57% to almost complete, and absorption of TPI is ≥ 27% to < 50% (Study TPU-TAS-102-108). Neither FTD nor TPI is a substrate or inhibitor of MDR1. Therefore, drug interactions with TAS-102 mediated by human P-gp are unlikely.
- In place of an absolute bioavailability study, the sponsor submitted a single-dose relative bioavailability crossover study comparing tablets (20 mg x 3) to an oral solution (Study TPU-TAS-102-104). Based on the results for the $AUC_{0\text{-last}}$, the relative bioavailability (tablet/solution) was 100% (95% CI: 93%, 109%) for FTD and 96% (90% CI: 86%, 107%) for TPI. The 90% CI for the geometric mean ratio of the C_{max} for TPI (90% CI: 89%, 116%) was completely enclosed within the standard bioequivalence interval of 80% to 125%, but marginally outside the bioequivalence interval for the 90% CI for the geometric mean ratio of the C_{max} for FTD (90% CI: 79%, 95%). Based on the overall results of the relative bioavailability study, the TAS-102 tablets used in the study (Late CTM; 20 mg) are considered to optimally formulated.
- The effect of food on the PK of FTD and TPI was investigated in a single dose (35 mg/m^2) crossover study in Japanese patients (Study J004-10040040). The geometric mean ratios (fed/fasting) for FTD were 96% (90% CI: 86%, 107%) for the $AUC_{0\text{-inf}}$ and 61% (90% CI: 50%, 73%) for the C_{max}. The geometric mean ratios (fed/fasting) for TPI were 56% (90% CI: 48%, 64%) for the $AUC_{0\text{-inf}}$ and 58% (90% CI: 44%, 66%) for the C_{max}. The study showed that, compared to the fasting state, food significantly reduced the $AUC_{0\text{-inf}}$ and C_{max} values of TPI by 44% and 42%, respectively, and the C_{max} value of FTD by 39%. The significantly lower C_{max} values for FTD and TPI in the fed compared to the fasted state suggest that potential toxicities of TAS-102 might be reduced if the product is administered with food.
- The effect of TPI on the bioavailability of FTD was investigated following a single-dose of TAS-102 containing FTD 35 mg/m^2 and TPI versus a single-dose of FTD 35 mg/m^2 alone (Study TPU-TAS-102-102). Based on the ratio of the geometric mean estimates (TAS-102/FTD), the FTD $AUC_{0\text{-last}}$ was approximately 37 fold higher following TAS-102 than FTD alone, and the FTD C_{max} was approximately 22 fold higher following TAS-102

than FTD alone. The sponsor comments that simple extrapolation based on the AUC values indicates that the dose of FTD alone that would be necessary to achieve the FTD AUC observed after administration of TAS-102 is 1295 mg/m^2 (that is, 35 mg/m^2 x 37). The sponsor reported that this oral dose of FTD is predicted to exceed the projected lethal dose for humans of 1194 mg/m^2, based on primate toxicology studies. The equivalent dose in monkeys was reported to be associated with severe gastrointestinal and haematologic toxicities. The study supports the rationale for a fixed dose combination product (FTD plus TPI) rather than FTD alone.

- The $AUC_{0\text{-}10h}$ of FTD increased more than dose proportionally over the dose range 15 to 35 mg/^{2} BD, while the $AUC_{0\text{-}10h}$ of TPI increased dose proportionally over the same dose range (Study J001-10040010). Following multiple doses of TAS-102 (35 mg/m^2 BD), the $AUC_{0\text{-}last}$ of FTD accumulated approximately 3 fold on Day 12 compared to Day 1 and the C_{max} accumulated approximately 2 fold (Study TPU-TAS-102-102). However, there was no further accumulation of FTD in subsequent cycles. There was no accumulation of TPI following multiple doses of TAS-102. The mechanism for accumulation of FTD following multiple daily dosing has not been identified.
- Both the inter-subject and intra-subject variability in the PK of TAS-102 were investigated in Study TPU-TAS-102-104. The inter-subject variability of both FTD and TPI was high, with CV% values for $AUC_{0\text{-}last}$ and C_{max} being 60.9% and 64.3%, respectively, for FTD and 54.3% and 58.6%, respectively, for TPI. The intra-subject variability of both FTD and TPI was moderate to low, with CV% values for $AUC_{0\text{-}last}$ and C_{max} being 16.4% and 25.4%, respectively for FTD, and 28.9% and 36.0%, respectively, for TPI.
- In Study TPU-TAS-102-102, the apparent volume of distribution was 21 L for FTD and 333 L for TPI following a single-dose of TAS-102 (35 mg/m^2). The population PK study estimated that the apparent volume of distribution (Vd/F) was 10 L (CV = 25%) for FTD and 192 L (CV = 63%) for TPI following multiple dosing with TAS-102 (Study 12DA25). In the Population PK model, BSA was identified as a significant covariate of Vd/F for both FTD and TPI. No other tested covariates in the population PK model had a clinically meaningful effect on the Vd/F of FTD or TPI. Protein binding of FTD in vitro was greater than 96% and was independent of concentration, while protein binding of TPI did not exceed 8% in the presence or absence of FTD (Study AE-2350-25). FTD binds mainly to human serum albumin. Plasma protein binding of FTY (main metabolite of FTD) was approximately 70% (Study 15DB01). The human blood/plasma concentration ratios of both FTD and TPI were approximately 0.6, and were independent of concentration. The results for the human blood/plasma concentration ratios indicate that both FTD and TPI are distributed mainly to the plasma fraction.
- In vitro human biomaterial studies showed that FTD and TPI are not metabolised by CYP enzymes. The in vitro studies demonstrated that FTD is metabolised primarily to FTY by thymidine phosphorylase (TPase), and that TPI is metabolised primarily to 6-hydroxymethyl uracil (6-HMU). The primary method of elimination of FTD is by metabolism to FTY in the intestinal tract and/or liver, while the primary method of elimination of TPI is by urinary excretion of unchanged TPI. In the mass balance Study TPU-TAS-102-108, the absorbed FTD was metabolised and then excreted in the urine as FTY and FTD glucuronide isomers. In the mass balance Study TPU-TAS-102-108, the absorbed TPI was excreted largely unchanged in the urine along with its major metabolite 6-HMU. The sponsor reports that the metabolites of FTD and TPI are pharmacologically inactive.
- In Study TPU-TAS-102-102, following single dose and multiple dose administration of TAS-102 (35 mg/m^2), the mean terminal half-lives on Day 1, Cycle 1 and Day 1, Cycle 12 were 1.4 and 2.1 hours, respectively, for FTD, and 2.1 and 2.4 hours,

respectively, for TPI (Study TPU-TAS-102-102). In this study, the apparent oral clearance (CL/F) values were 10.5 L/h for FTD and 109.3 L/h for TPI. In the population PK Study 12DA25, the CL/F values were 2.93 L/h (CV = 32.2%) for FTD and 88.7 L/h (CV = 44.3%) for TPI. In the population PK analysis, baseline creatinine clearance (CLCR) was identified as a significant covariate for CL/F of both FTD and TPI, while baseline serum albumin (ALB) was identified as a significant covariate for CL/F of FTD (negative correlation possibly due to high protein binding of FTD).

- In Study TPU-TAS-102-104, urinary excretion was 1.5% for unchanged FTD, 19.2% for FTY (main metabolite of FTD), and negligible for other metabolites of FTD, while urinary excretion of unchanged TPI was 29.3%. The renal clearance (CLr) was 2.29 mL/min for FTD, 40.85 mL/min for FTY (main metabolite of FTD) and 292.67 mL/min for TPI. The CLr for TPI (approximately 293 mL/min) was approximately 3 fold greater than the CLcr for TPI (approximately 105 mL/min), indicating that TPI undergoes renal tubular secretion.
- In the mass balance Study TPU-TAS-102-108, the total cumulative elimination of TRA derived from (^{14}C)-FTD was approximately 60% of the administered dose. The majority of recovered TRA was eliminated into urine within 24 hours after oral administration (approximately 55%), and excretion into faeces and expired CO_2 was approximately 2.6% and 2.4%, respectively. Approximately 90% of plasma TRA was bound to plasma protein, and extractable TRA (6.67%) consisted of 52.7% FTD and 33.2% of FTY. The PK data showed that FTD and FTY accounted for approximately 12% of the total AUC of TRA in plasma. In urine, excreted TRA consisted of 45.9% FTY, 2.41% FTD, and 33.3% FTD glucuronide isomers. In faeces, multiple radioactive peaks were observed (trace levels). The major metabolite of FTD in the extractable fraction in plasma and urine was FTY. The overall recovery of radioactivity derived from (^{14}C)-FTD administered with TAS-102 was relatively poor (approximately 60%) and is probably due to covalent binding to proteins.
- In the mass balance Study TPU-TAS-102-108, recovered TRA of (^{14}C)-TPI was approximately 77% of the administered dose, and consisted of approximately 27% urinary excretion and 50% faecal excretion. The overall recoveries were > 85% and reproducible for 3 of the 4 patients, whereas 1 patient exhibited extremely poor recovery at 36.3% of the dose. In plasma, extractable TRA consisted of 53.1% TPI and 30.9% 6-HMU, in urine, extractable TRA consisted of 79.1% TPI and 14.0% 6-HMU, and in faeces, extractable TRA consisted of 48.2% TPI and 34.4% 6-HMU. It was noted that the 6-HMU metabolite appeared in plasma or in blood after disappearance of TPI, which according to the sponsor may suggest that 6-HMU was slowly produced via a metabolic pathway other than hepatic metabolism. Overall, TPI was the major moiety in plasma, urine, and faeces and 6-HMU was the major metabolite of TPI in these 3 matrices. No metabolites of TPI other that 6-HMU were detected at concentrations of greater than 5% in the plasma, urine or faeces. Based on TRA derived (^{14}C)-TPI excreted into the faeces and the urine, it can be estimated that the absorbed fraction of TPI was likely to be at least 27% but not greater than 50%. This suggests that the primary site of the inhibitory action of TPI on TPase might be in the intestinal tract rather than the liver.
- The population PK Study 12DA25, indicated that age, gender and race were not significant covariates for either Vd/F or CL/F of both FTD or TPI. There was no dedicated clinical study investigating the effects of hepatic impairment on the PK of TAS-102. Data from RECOURSE suggests, the mild hepatic impairment is unlikely to significantly affect the PK of FTD or TPI. There were no data in patients with moderate or severe hepatic impairment. There was no dedicated clinical study investigating the effects of renal impairment on the PK of TAS-102. Data from RECOURSE suggests that

both mild and moderate renal impairment can increase exposure. There were no data in patients with severe renal impairment or ESRD.

- No dedicated clinical drug-drug interaction studies were conducted. In vitro studies with human biomaterials were reported to show that neither FTD nor TPI are metabolised by the broad range of CYP enzymes tested. In addition, FTD and FTY were reported not to inhibit or induce the CYP enzymes tested. It was also reported that the in vitro data showed that TPI did not inhibit or induce the CYP enzymes tested. However, in the CHMP expressed its concern that that the maximum concentration of TPI used in the CYP induction studies was too low to definitively exclude TPI mediated induction of CYP enzymes. The sponsor has indicated that it will conduct an additional CYP study investigation induction at higher TPI concentrations.
- In vitro, FTD was reported not to be a substrate for MDR1, OATP1B1, OATP1B3 and BCRP, or to be an inhibitor of these transporters. In vitro, TPI was reported not to be a substrate for OAT1, OAT3, MDR1, and BCRP, or to be an inhibitor of these transporters. However, TPI in vitro was reported to be a substrate for, and an inhibitor of, the efflux transporters OCT2 and MATE1 at concentrations substantially higher than those anticipated in plasma in clinical practice. Therefore, TPI at recommended clinical doses is unlikely to cause drug-drug interactions due to inhibition of OCT2 and MATE1. However, as TPI is reported to be a substrate for OCT2 and MATE1 it is possible that urinary excretion of TPI might be reduced when TAS-102 is administered with inhibitors of these transporters. In vitro studies were reported to show that FTD is a substrate for the nucleoside transporters CNT1, ENT1 and ENT2.

Population pharmacokinetics

Critical summary of key models of the PPK analyses

All models which were presented in the reports were provided by the sponsors for the population PK studies of FTD and TPI. However only the base and the final model were repeated using the software NONMEM version 7.3 and PsN version 3.7.6.

No deviations from the submitted results presented in the report and provided in the model result files by the sponsors were found. The results submitted in the report can be confirmed according to the evaluation performed.

Main comments from the model evaluation are:

- The sponsors may wish to revaluate the 2 compartment model presented for FTD, as some numerical instability was noted and results could not be matched. However, it is still evident that the presented 1 compartment model is likely the more appropriate distribution model.
- Several questions were raised throughout the report regarding covariate inclusion, more models may need to be tested by the sponsors to answer questions raised (see below for more details).
- The transit compartment model code may need to be reassessed by the sponsors, as the number of transit compartments can be estimated and doesn't need to be fixed as the sponsors have done. This may improve the absorption model and influence estimates of Vd/F and CL/F.

Critical summary of the evaluation of report TAS-102 against Guideline CHMP/EWP/185990/06

The sponsors report titled 'Population pharmacokinetic analysis for FTD and TPI following TAS-102 administration in selected clinical studies in patients with solid tumor cancers' has been reviewed using the 'Guideline on Reporting the Results of Population

Pharmacokinetic Analyses CHMP/EWP/185990/06' published by EMA and adopted by TGA.

The report has been assessed and has been found to generally agree with the requirements outlined in the guidelines. A detailed critical summary, addressing each of the points, can be found below. Overall, the report was found to use appropriate data, method and evaluation standards for a population PK analysis.

Main comments are:

- There was no specific mention of how the pharmacokinetic predictions and covariate relationships generated by the population PK analysis might be used or why the investigators wanted to investigate individual drug exposures in patients enrolled in the Phase III Study TPU-TAS-102-301, using the established population PK parameters.
- Setting below lower limit of quantitation (LLOQ) data to zero is not the optimal way of handling such data and can lead to bias parameter estimates. No information was provided on the percentage of concentration values that were below the LLOQ therefore it is not possible to comment on the potential impact of this on modelling outcomes. Have these values really been set to zero, or deleted from the data set? Both methods would result in bias and are not appropriate at higher rates of LLOQ samples. Even with lower percentages of LLOQ samples setting these values to zero is not appropriate.[12]
- Covariates to be tested for inclusion in the model were listed, however limited rationale for testing these covariates based on, for example, biological, pharmacological and/or clinical plausibility was provided; this is not in line with EMEA guidelines.
- No equation was provided for calculation of BSA. It is not clear how the covariate 'performance status' was accessed. The sponsors should clarify further.
- Measurement of FTY in plasma and FDT, FTY and TPI in urine samples was briefly mentioned in the analysis plan and/or the report. The sponsors may wish to clarify the purpose (if any) of FTY plasma and FDT, FTY and TPI urine measurements and how (if at all) they were applied during the PPK analysis.
- An overall appreciation of the distribution of concentration-time points in relation to the TAD could not be easily obtained from the report. It would also have been helpful to have a graphic of FTD and TPI plasma concentration versus time after dose across all individuals in the PPK analysis in the one plot.
- Information regarding patient drop-outs during the studies could not be found in the report.
- Diagnostic plots lacked trend lines making them more difficult to interpret. It would have been useful to have a plot of CWRES versus TAD (as well as TIME). These plots should be reconsidered when shrinkage is above 25%, as they are of limited diagnostic value.[13]
- No justification was provided for why BSA was selected as the typical body size parameter instead of body weight and height in the report. The sponsors may wish to clarify.

[12] Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn.* 28: 481-504 (2001).
[13] Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. *AAPS J.* 11: 558-69 (2009).

- Values of affected parameters at the extremes and/or the 5th to 95th percentiles of the covariate range where not given numerically. Please provide these to obtain a better understanding of the covariate effects on CL/F in particular.
- TPI is an inhibitor of TPase and co-administration with FTD prevents the rapid degradation of FDT in the body. Did the sponsors consider testing TPI exposure and its influence on FDT pharmacokinetics or linking the TPI and FDT pharmacokinetic models? The sponsor may which to clarify further, why FDT exposure was not considered as a covariate on CL/F or on F for TPI? (Also refer to comment (bullet point) 3 above.
- Simulations for model evaluation would have been easier to interpret if distinct lines had been included on the VPCs representing the 5th, 50th and 95th percentile of the observations and simulations, respectively; and a shaded region had been included represent the 90% confidence intervals of the simulated 5th, 50th, and 95th percentiles from simulations. Prediction and variance corrected VPC's for the combined data set should have been provided as well.[14]
- While estimation of individual drug exposures in patients enrolled in the Phase III Study TPU-TAS-102-301 using the established PPK parameters was an objective of this study there was no specific section in the report dedicated to presenting these results or in interpreting their meaning. Please provide more results and interpretation of the results in regard to the second aim of the analysis.
- The discussion in the report analysis primarily addresses the clinical relevance of covariate influences. The discussion did not greatly consider how well the results of the population PK analysis agree with previously obtained information. A discussion on how the results of the analysis will be used (for example, to support labelling, individualise dosage, or define additional studies) was not provided.
- BSA was a significant covariate for Vd/F in both final models of FTD and TPI.
- Other body size descriptors were not tested and therefore it is known whether any other descriptor would have been more influential. The sponsors made the comment that 'BSA dosing of TAS-102 is adequate to reduce the variability of exposure of FTD and TPI.' It should be noted however whether BSA dosing is adequate (or not) will also depend on the extent of unexplained variability that remains after BSA has been taken into consideration and the width of TAS-102's therapeutic window. Whether the influence of any body size descriptors on CL/F were tested is not clear. This should be reassessed by the sponsors.
- An exponential relationship was used to describe the influence of BSA on Vd/F in both final models of FTD and TPI, however the exponent estimated for the relationship was close to 1, in particular for FTD. The median of the bootstrap result reported was even closer to 1 and the 95%CI included 1. Was a linear model tested? How did this compare to the exponential model? This comment is applicable for both FTD and TPI.
- The sponsors made the comment that 'PK of FTD and TPI are not expected to be affected by race.' It should be noted that the dataset consisted of 61% Caucasian and 26% Asian (mainly Japanese) patients. The effect of races other than Caucasian and Asian on the PK of TAS-102 is unlikely to be determinable from this study.
- CLCR of patients in the dataset analysed ranged from 35 to 200 mL/min. However, it is not entirely clear what proportion of patients in the dataset had mild, moderate and severely impaired renal function. If few patients in the dataset had very poor renal

[14] Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J.* 13: 143-51 (2011).

function it would be difficult to extrapolate conclusions to these individuals. It should be noted that from the sponsors' calculations patients with mild renal impairment were reported to have 108% to 132% greater exposure to TAS-102 than patients with no renal impairment, whether this is clinically significant will depend on the pharmacodynamic properties of TAS-102 and its therapeutic window and cannot be entirely determined from the PPK analysis. There is no section in the analysis report that explains how these calculations were performed. The sponsors should clarify.

- The sponsors made the comment that 'the PK of FTD and TPI are not expected to be affected by hepatic function'. Liver function parameters including SGOT, SGPT, ALP, and BIL were not significant covariates for PK parameters of either FTD or TPI in the population PK analysis. However, it is not entirely clear what proportion of patients in the dataset had mild, moderate and severely impaired liver function. If few patients in the dataset had hepatic impairment then the effect of hepatic impairment on the PK of TAS-102 cannot be entirely determined from the population PK analysis.
- There was no discussion on how drop-outs affected the results of the study.
- ALB was added as a covariate on CL/F for FTD and related to protein binding. Changing ALB levels are likely to influence FDT total drug concentrations and free drug fraction but possibly not free drug concentrations on re-establishment of equilibrium. The effect of changing ALB is likely to be on both total drug CL/F and V/F, possibly other more suitable protein binding models could have been utilised. Please justify why ALB was added only as a covariate on CL/F and discuss whether you expected changes in ALB to influence free drug exposure.
- The number of compartments in a transit compartment absorption model can be estimated. There is no need to fix this to discrete numbers and test them all. As an example, see Hennig et al.[15] The models should be revaluated in regard to the number of transit compartments, particularly for the FTD model, which showed a further decrease in OBJ when using 5 instead of 4 transit compartments.

While results of the final population PK models for both FTD and TPI could be replicated in this evaluation, assessment of the report raised multiple questions in regard to the appropriateness of some model building techniques. Clarification is required on the points listed above to gain certainty on the model appropriateness before conclusions can be drawn from the final models. No simulations were provided to evaluate the clinical impact of covariates included in the final model to support any claims made.

Pharmacodynamics

Studies providing pharmacodynamic data

The submission included the following studies with pharmacodynamic data:

- An exploratory PK/PD report of data collected during the pivotal Phase III study (RECOURSE) relating to exposure-efficacy outcomes and exposure-safety outcomes. This report was presented (sponsor's response to the CHMP Day 120 List of Questions).
- An analysis of cardiac safety, including the effect of TAS-102 on the QTc interval, was presented in Study TPU-TAS-102-103.

[15] Hennig S, et al. Population pharmacokinetic drug-drug interaction pooled analysis of existing data for rifabutin and HIV PIs. *J Antimicrob Chemother.* 71: 1330-40 (2016).

- An analysis of the correlation between haematologic toxicity and both the dosage and the pharmacokinetics of TAS-102 was presented in Study J001-10040010.

Evaluator's conclusions on pharmacodynamics

PK/PD efficacy analyses; OS and PFS

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

PK/PD safety analyses

- In the RECOURSE study, the incidence of both Grade ≥ 3 neutropaenia and any Grade ≥ 3 drug related AE was higher (> 10%) in the FTD high AUC group compared to the FTD low AUC group, and any dose reduction due to safety events was also higher in the FTD high compared to the low AUC group (23% versus 9%, respectively). However, no marked differences in Grade ≥ 3 neutropaenia, any Grade ≥ 3 drug related AEs or dose reduction due to safety events were observed between the TPI high and low AUC groups.
- In the RECOURSE study, mean changes in neutrophil count (10^9/L) from Baseline at Cycle 1 Last Assessment were similar in the FTD low and high AUC groups (-2.225 versus -2.260, respectively) and in the TPI low and high AUC groups (-2.168 versus -2.316, respectively). Mean changes in neutrophil count (10^9/L) from Baseline at the Cycle 1 Nadir were similar in the FTD low and high AUC groups (-3.105 versus -3.331, respectively), and marginally lower in the TPI low AUC group compared to the TPI high AUC group (-2.952 versus -3.483, respectively).
- In Study J100-10040010, there were significant correlations between percent decreases in both the white blood cell count and the neutrophil count and dosage in all cycles tested, while no correlations were seen between dosage and percent changes in platelet counts and haemoglobin. There were significant correlations between decreased white blood cell count and neutrophil count and the C_{max} and $AUC_{0\text{-}10h}$ of FTD, FTY and TPI in Cycle 1 (Day 12), with similar results being found in all other cycles tested. There were significant correlations between decreased platelet count and the C_{max} and AUC0-10h of TPI in Cycle 1 (Day 12) and all other cycles tested, while the $AUC_{0\text{-}10h}$ of FTD showed a significant correlation with decreased platelet in all cycles tested. There was a significant correlation between percent decrease in haemoglobin and the $AUC_{0\text{-}10h}$ of TPI in Cycle 1.

Cardiac safety; QTc prolongation and arrhythmogenic AEs

- The data from the Phase I Study TPU-TAS-102-103 undertaken in the USA and the UK showed that clinically significant effects of TAS-102 on QTc prolongation are unlikely to occur in patients treated with the medicine at the proposed dosed for the proposed indication. Overall, the cardiac safety data from Study TPU-TAS-102-103 showed that TAS-102 does not appear to be arrhythmogenic, based on both the absence of clinically significant QTc prolongation and no reported AEs of ventricular tachycardia, ventricular fibrillation, syncope, or seizure.

Dosage selection for the pivotal studies

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

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

Table 4: Initial Phase I dose-finding studies conducted in the US, legacy studies

Study	N	Daily dose mg/m²/day	Dosing frequency	Regimen	Prior therapies (median)	Malignancy % patients	MTD mg/m²/day	DLT
TAS102-9801	14	50, 60, 100	QD	2 weeks with 1 week rest, repeated every 3 weeks.	4	CRC 100%	50	Granulo-cytopaenia
TAS102-9802	24	50, 70, 80, 110	QD	5 days with 2 days rest for 2 weeks, repeated every 4 weeks	2.5	CRC 83.3%	100	Granulo-cytopaenia
TAS102-9803	39	100, 110, 120, 130. 140, 150, 160, 170, 180.	QD	5 days every 3 weeks.	4	CRC 82.1%	160	Granulo-cytopaenia and others.[a]
TAS102-9804	19	50, 60, 80	BD	5 days with 2 days rest for 2 weeks, repeated every 4 weeks	5	BC 100%	50	Granulo-cytopaenia and others.[b]
TAS102-9805	15	60, 70, 80	TDS	5 days with 2 days rest for 2 weeks, repeated every 4 weeks	3	CRC 100%	70	Granulo-cytopaenia and others.[c]

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

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

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

The safety profile observed with TAS-102 in the Western (US) Study TPU-TAS-102-102 was consistent with that observed using the same TAS-102 dose regimen (35 mg/m^2 BD) in a Phase II study in Japanese patients (n = 172) with mCRC (Study J003-10040030). In the FAS population in the Japanese Phase II study, median overall survival (OS) was 9.0 months in the TAS-102 group and 6.6 months in the placebo group (hazard ratio (HR) = 0.56 (95% CI: 0.39, 0.81), p = 0.0011). Progression free survival (PFS) based on Independent Reader assessments was 2.0 months in the TAS-102 group and 1.0 month in the placebo group (HR = 0.41 (95% CI: 0.28, 0.59), p < 0.0001). The disease control rate (DCR; partial response (PR) + stable disease (SD)) in the TAS-102 group was 43.8% compared to 10.5% in the placebo group (p < 0.0001). The most commonly reported side effects in the Japanese Phase II study were bone marrow suppression and gastrointestinal related events. The toxicity profile seen in Japanese patients was qualitatively similar to that observed in the US Phase I Study TAS-102-101). The most frequent Grade 3 or 4 AE in both studies was neutropaenia. In the Japanese study, Grade 3 and 4 neutropaenia occurred in 31.9% and 18.6% of patients, respectively, and in the Western (US) study Grade 3 and 4 neutropaenia occurred in 40.9% and 13.6% of patients, respectively.

Based on the results obtained in the Japanese Phase II study in mCRC (Study J003-10040030), and the tolerability of the 35 mg/m^2 BD regimen demonstrated in the US Phase I study in patients with CRC (Study TPU-TAS-102-101), a Phase III global study of TAS-102 (35 mg/m^2 BD) in refractory mCRC colorectal cancer was initiated (RECOURSE/ Study TPU-TAS-102-103).

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

Efficacy

Studies providing efficacy data

- Pivotal efficacy Study TPU-TAS-102-301 (RECOURSE): 'A randomised, double blind, Phase III study of TAS-102 plus best supportive care versus placebo plus best supportive care (BSC) in patients with metastatic colorectal cancer refractory to standard chemotherapies. The study is also referred to as RECOURSE.'
- Supportive Study J003-10040030: 'A placebo controlled, multicentre, double blind, randomised, Phase II study of TAS-I02 in patients with unresectable advanced or

recurrent colorectal cancer who have had 2 or more chemotherapy regimens and who are refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin'.

Evaluator's conclusions on efficacy

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

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

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

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

RECOURSE (pivotal Phase III study)

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

In RECOURSE, patients with mCRC refractory to standard chemotherapies were randomised to double-blind treatment with TAS-102 plus BSC (n = 534) or placebo plus BSC (n = 266). The primary efficacy analysis was comparison of OS between the 2 treatment arms, with survival follow up data being obtained through the date of the 571st death observed in the study. At the cut-off date for the primary analysis of OS (24 January 2014) there had been a total of 574 deaths, including 364 (68.2%) in the TAS-102 arm and 210 (78.9%) in the placebo arm.

The median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The modest increase in OS of 1.8 months in the TAS-102 arm compared to the placebo arm

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

The modest improvement in OS in the TAS-102 arm compared to the placebo arm needs to be interpreted in the context of patients with mCRC resistant to standard treatments. Patients were required to have received at least 2 prior regimens of standard chemotherapies for mCRC refractory. Standard chemotherapy must have included all of the following agents approved in each country in which patients were enrolled: fluoropyrimidines, irinotecan and oxaliplatin; an anti-VEGF monoclonal antibody (bevacizumab); and at least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients. Of the total patient population, the proportion of patients who had received 1, 2, 3 and ≥ 4 prior regimens for mCRC was 3%, 22.8%, 27.8% and 46.5%, respectively. Of the total population, 93.8% were reported as being intolerant to fluoropyrimidine in their last prior regimen.

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

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

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

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

Study J003-10040030 (supportive Phase II study)

At the cut-off date for the OS analysis in Japanese patients, death had occurred in 75 patients in the TAS-102 group (67.0% (75/112)) and 48 patients in the placebo group (84.2% (48/57)). The median OS in the FAS was 9.0 months in the TAS-102 group and 6.6 months in the placebo group: HR = 0.56 (95% CI: 0.39, 0.81); p = 0.0011, stratified log-rank test. The difference in median OS between the 2 treatment groups was 2.4 months in favour of the TAS-102 group. This relatively small improvement in OS should be interpreted in the context of heavily pre-treated patients with refractory mCRC.

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

Safety

Studies providing safety data

The key integrated safety data were presented in an Integrated Summary of Safety (ISS) for all patients with mCRC who received TAS-102 at a dose of 35 mg/m^2 BD (Safety Data Group 1; n = 761) and for all patients in the 2 placebo controlled studies (RECOURSE; StudyJ003-10040030) who received TAS-102 (n = 646) or placebo (Safety Data Group 2; n = 656 (TAS-102), n = 322 (placebo)). The studies included in Safety Data Groups 1 and 2 are summarised below.

Table 5: Overview of clinical studies included in the integrated safety database, patients with mCRC receiving starting dose of TAS-102 35 mg/m²

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

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

In addition, to Safety Data Groups 1 and 2, the ISS also included Safety Data Groups 3 and 4. Safety Data Group 3 included serious adverse events (non-integrated) from Safety Data Groups 1 and 2, in addition to the following sources at the SAE cut-off date of 24 July 2014 (cumulative data except as noted): (i) mCRC patients in Group 1 and 2 remaining on TAS-102 35 mg/m² BD monotherapy as of study data cut-off dates (incremental data from these dates to 24 July 2014); (ii) patients in Group 1 and 2 who had diagnoses other than CRC and/or who received treatment other than TAS-102 35 mg/m² BD monotherapy; and (iii) other non-integrated studies including completed studies in patients who had diagnoses other than CRC and/or who had received treatment other than TAS-102 35 mg/m² BD monotherapy, ongoing studies for which a final report had not been generated, and investigator-initiated studies.

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

Post-marketing data

The first country in which trifluridine/tipiracil (Lonsurf) was approved for marketing was Japan. The medicine was approved in Japan on 24 March 2014 and launched for marketing on 26 May 2015. The approved indication in Japan was amended on 20 March 2015 to

include 'unresectable advanced or recurrent colorectal cancer', based on the results of RECOURSE. The sponsor estimates that cumulative exposure in Japan from May 2014 to June 2015 is approximately 7037 patients.

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

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

In a document titled 'Post-marketing experience in patients with unresectable advanced or recurrent colorectal cancer', the sponsor stated that:

> *'(T)o date, TAS-102 has been authorised for use in two countries, Japan (March 24, 2014) and USA (September 22, 2015). There have been reports of interstitial lung disease in patients receiving Lonsurf in post-approval use in Japan.'*

Evaluator's conclusions on safety

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

In RECOURSE, the safety population included 533 patients with mCRC who had been treated with TAS-102 (mean of 12.7 and median of 6.7 weeks of exposure) and 265 patients in the placebo group (mean of 6.8 and median of 5.7 weeks of exposure). The mean ± SD (and median) number of 28 day treatment cycles initiated in the 2 treatment groups was 3.4 ± 2.56 (median 2.0) in the TAS-102 group and 2.3 ± 1.49 (median 2.0) in the placebo group. There are limited data on patients who have been treated for longer than 6 months, with a maximum of 6 x 28 day treatment cycles being initiated in only 37 (6.9%) patients in the TAS-102 group and 3 (1.1%) of patients in the placebo group. The small number of 28-day cycles initiated in both treatment groups, and the small number of patients for whom a maximum of 6 cycles were initiated reflects the relatively poor prognosis of the patients with refractory mCRC included in the pivotal study.

Overall, the total number of weeks of exposure in RECOURSE was approximately 4 fold longer in the TAS-102 group than in the placebo group (6743 versus 1791 weeks respectively). The notably longer period of exposure in the TAS-102 group compared to the placebo group should be taken into account when comparing the AE data between the

2 treatment groups. No safety data could be identified in the study report comparing safety outcomes in the 2 treatment groups adjusted for duration of exposure.

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

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

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

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

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

First Round Benefit-Risk Assessment

First round assessment of benefits

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

In addition, the median OS was consistently longer in the TAS-102 group compared with the placebo group across all 3 stratification analyses (that is, KRAS status (wild versus mutant type); time since diagnosis of first metastasis (< 18 months versus ≥ 18 months); region (Asia versus Western)). Furthermore, pre-specified analyses of OS in various subgroups (including age, gender and race) consistently favoured longer survival in the TAS-102 group compared to placebo.

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

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

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

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

First round assessment of risks

The risks of TAS-102, given the proposed usage, are considered to be favourable. The adverse events associated with TAS-102 are consistent with a medicine containing an

antineoplastic thymidine-based nucleoside analogue (that is, trifluridine), which interferes with DNA synthesis and inhibits cell proliferation.

Overall, the safety data from the pivotal Phase III study (RECOURSE) demonstrated that the safety profile of TAS-102 was inferior to the safety profile of placebo. The most frequently reported risks associated with TAS-102 were myelosuppression (anaemia, leukopaenia, neutropaenia, febrile neutropaenia and thrombocytopaenia), gastrointestinal events (nausea, vomiting and diarrhoea), and infections (predominantly nasopharyngitis, urinary tract infection, and upper respiratory tract infection). In general, the adverse events associated with TAS-102 were manageable by treatment interruption, delays in cycle initiation, and reductions in dose rather that by treatment discontinuation.

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

Haematologic toxicities

The risk of experiencing a 'blood and lymphatic disorder' (SOC) was 5.2 fold greater for patients in the TAS-102 group compared to patients in the placebo group (57.0% versus 10.9%), while the risk of experiencing a Grade ≥ 3 AE in this SOC was 8.5 fold greater (35.5% versus 4.2%). The higher incidence of AEs in this SOC in the TAS-102 group compared to the placebo group was primarily due to the increased risk of AEs associated with myelosuppression. There were no deaths in either of the 2 treatment groups reported for haematologic AEs.

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

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

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

Gastrointestinal toxicities

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

Infections and infestations

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

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

Thromboembolic events (arterial or venous)

Arterial or venous thromboembolic events (all Grades) were reported more frequently in patients in the TAS-102 group than in the placebo group (3.9% versus 2.3%, respectively), and the majority of events in both groups were ≥ Grade 3 in severity (2.1% versus 1.5%, respectively). The major difference between the 2 treatment groups related to the higher incidence of pulmonary embolism (all Grades) in the TAS-102 group compared to the

placebo group (1.7% (n = 9) versus 0% (n = 0)). All pulmonary embolisms in the TAS-102 group were ≥ Grade 3 in severity, and included one fatal case. Despite the higher patient incidence of pulmonary embolism in the TAS-102 group compared to the placebo group, deep venous thrombosis was reported in a similar proportion of patients in both treatment groups (0.6% versus 0.8%, respectively).

Other risks of special clinical interest

Other risks (any AEs (Grade ≥ 3 AEs)) of special clinical interest reported a similar percentage of patients in the TAS-102 and placebo groups, respectively, were: bleeding (8.1% (0.6%) versus 8.7% (3.0%)); 'cardiac disorders', SOC (3.9% (0.8%) versus 4.5% (1.1%)); 'hepatobiliary disorders', SOC (10.3% (6.2%) versus 10.6% (6.8%)); 'neoplasms benign, malignant and unspecified (including cysts and polyps', SOC (8.6% (0.8%) versus 13.2% (3.4%)); 'nervous system disorders' (21.2% (2.1%) versus 19.6% (4.2%)); 'renal and urinary disorders', SOC (13.1% (2.3%) versus 11.3% (3.0%)); 'immune system disorders', SOC (0.4% (0%) versus 0.4% (0.4%)), with 1 anaphylactic reaction being reported in the placebo group (none in the TAS-102 group) and 1 hypersensitivity reaction being reported in the TAS-102 group (none in the placebo group).

'Skin and subcutaneous tissue disorders', SOC were reported more frequently in patients in the TAS-102 group compared to the placebo group (23.8% versus 18.1%), with the greatest difference between the 2 groups being due to increased alopecia in the TAS-102 group compared to the placebo group (6.8% versus 1.1%). Grade ≥ 3 AEs in this SOC were reported infrequently in both treatment groups (0.4%, TAS-102 (1 x decubitus ulcer, 1 x urticaria); 0.8%, placebo (1 x pruritus, 1 x rash). There were no reported cases of Stevens-Johnson syndrome or toxic epidermal necrolysis in either treatment group.

Commonly occurring AEs (PT)

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

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

Commonly occurring Grade 3 or Grade 4 AEs

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

Deaths and other serious adverse events

Deaths reported after the first dose of study medicine and ≤ 30 days after the last dose occurred notably more frequently in the placebo group than in the TAS-102 group (12.4% versus 6.6%). Fatal AEs were reported in 3.2% (n = 17) of patients in the TAS-102 group and 11.3% (n = 30) of patients in the placebo group. The most frequently reported fatal AE

in both treatment groups was general physical health deterioration, which was reported in 6 patients (1.1%) in the TAS-102 group, and 8 (3.0%) patients in the placebo group. In the TAS-102 group, 2 patients died due to hepatic failure, and 2 died due to acute renal failure. In the placebo group, 6 patients died due to hepatic failure, 1 died due to renal failure and 1 died due to renal impairment. One patient in the TAS-102 group and 4 patients in the placebo group had fatal AEs of dyspnoea. All other fatal AEs occurred in 1 patient each. The only treatment-related death occurred in 1 patient in the TAS-102 group (Klebsiella pneumonia/septic shock).

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

Discontinuations due to AEs

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

Dose reductions due to AEs

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

Treatment interruptions/delay or reduction due to AEs

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

Clinical laboratory

Laboratory haematological Grade ≥ 3 abnormalities were reported more frequently in patients in the TAS-102 group than in the placebo group for the following parameters - neutropaenia (37.9% versus 0%), lymphocytopaenia (21.5% versus 10.0%), leukopaenia (21.4% versus 0%), anaemia (18.2% versus 3.0%), and thrombocytopaenia (5.1% versus 0.4%). The only laboratory clinical chemistry abnormality of note was a greater incidence of hyperglycaemia ≥ Grade 3 in patients in the TAS-102 group compared to the placebo

group (6.4% versus 2.8%). There were no marked differences between the 2 treatment groups as regards the patient incidence of hepatobiliary clinical chemistry abnormalities, and no evidence of drug induced liver injury associated with TAS-102. There were no marked differences between the 2 treatment groups as regards the patient incidence of renal clinical chemistry abnormalities, and no evidence that TAS-102 is associated with renal toxicity. However, proteinuria (all grades) was reported more commonly in patients in the TAS-102 group than in the placebo group (4.1% versus 1.9%).

Vital signs and ECG

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

Special groups

There was an increased risk of AEs in patients aged ≥ 65 years of age treated with TAS-102 compared to patients aged < 65 years. In the TAS-102 group, patients aged ≥ 65 years had a higher incidence (difference of at least 5%) compared to patients aged < 65 years of anaemia (50.4% versus 32.1%), neutropaenia (32.9% versus 26.4%), neutrophil count decreased (31.2% versus 25.1%), platelet count decreased (21.4% versus 10.4%), white blood cell count decreased (31.6% versus 24.1%) and decreased appetite (41.9% versus 36.8%). Based on clinical laboratory assessments, patients aged ≥ 65 years in the TAS-102 group had a higher incidence than patients aged < 65 years (difference of at least 5%) of Grade 3 or 4 leukopaenia (25.5% versus 18.2%), Grade 3 or 4 neutropaenia (47.6% versus 30.3%), Grade 3 anaemia (26.0% versus 12.1%) and Grade 3 or 4 thrombocytopaenia (8.7% versus 2.4%).

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

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

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

First round assessment of benefit-risk balance

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

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

First round recommendation regarding authorisation

It is recommended that trifluridine/tipiracil be approved for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (clinical questions), the sponsor's responses, and the evaluation of these responses, please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

- No new efficacy data were submitted with the sponsor's post-first round response. Accordingly, the benefits of trifluridine/tipiracil (Lonsurf) are unchanged from those identified in the first round assessment.

Second round assessment of risks

- After consideration of the safety data submitted with the post-first round response, the risks of treatment with trifluridine/tipiracil (Lonsurf) remain substantially unchanged from those identified in the first round assessment. However, based on the results of the dedicated hepatic impairment study submitted with the response it is recommended that Lonsurf should not be used to treat patients with moderate or severe hepatic impairment. The single and multiple dose PK data for FTD suggested that exposure to this component of TAS-102 in patients with moderate hepatic impairment was comparable to exposure in patients with normal hepatic function. However, the single and multiple dose PK data for TPI suggested increased exposure to this component of TAS-102 in patients with moderate hepatic impairment compared to patients with normal hepatic function. The PK exposure data for patients with moderate hepatic impairment should be interpreted cautiously due to the small

number of patients in this patient population. Overall, it is considered that the PK data in patients with moderate hepatic impairment are too limited to allow clinically meaningful conclusions on dosage to be made for this patient population. Furthermore, the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment observed in the study raises concerns about the safety of Lonsurf in this patient population. The study supports the use of Lonsurf in patients with mild hepatic impairment without dose adjustment.

Second round assessment of benefit-risk balance

- The benefit-risk balance for trifluridine/tipiracil (Lonsurf) given the proposed usage remains favourable for the reasons identified in the first round assessment.

Second round recommendation regarding authorisation

It is recommended that trifluridine/tipiracil (Lonsurf) be approved for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[16]

- The sponsor has submitted EU Risk Management Plan (RMP) version 4 (dated 15 February 2016; data lock point (DLP) 24 July 2015) and ASA version 1 (date not provided) in support of this application.
- The sponsor provided an updated EU RMP (version 5, dated 16 February 2017) and an ASA (version 3.6, dated 13 March 2017) with the responses to the second round RMP recommendations.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 6, below.

[16] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
• All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
• Reporting to regulatory authorities;
• Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
• Submission of PSURs;
• Meeting other local regulatory agency requirements.

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Bone marrow suppression	✓	–	✓	–
	Gastrointestinal symptoms (nausea, vomiting and diarrhoea)	✓	–	✓	–
	Infection	✓	–	✓	–
	Use in patients with moderate renal impairment	✓	✓	✓	–
Important potential risks	Developmental toxicity/Use in pregnant and breast-feeding women	✓	–	✓	–
	Hyperbilirubinaemia in patients with baseline moderate to severe hepatic impairment[1]	✓	–	✓	–
Missing information	Use in patients with moderate to severe hepatic impairment[2]	✓	✓	✓	–
	Use in patients with severe renal impairment	✓	✓	✓	–
	Use in patients with cardiac disorders	✓	–	✓	–
	Use in patients in worse condition than ECOG 0 or 1.	✓	–	✓	–

1) Newly added to the summary of safety concerns; removed from summary of safety concerns in the EU RMP version 5; dated 16 February 2017; 2) Removed from the summary of safety concerns.

- 2 ongoing clinical trials are being conducted to assess the safety, tolerability and pharmacokinetics of Lonsurf in patients with renal or hepatic impairment.
- During the first round evaluation, the addition of 'medication error' as an important potential risk was recommended by the RMP evaluator. Additional risk minimisation activities, in the form of patient educational materials, were recommended to address this safety concern.
- ACSOM advised that 'medication error' should be included as an important potential risk in the summary of safety concerns, if not an important identified risk.
- In the sponsor's post-first round response, the sponsor has proposed a dosing calendar and a pack insert leaflet to mitigate the risk of medication error.
- In the sponsor's post-second round response, the sponsor maintained the decision of not including 'medication error' as an important potential risk.
- The sponsor has proposed to introduce different colours to the blister packs of different tablet strengths. The sponsor also confirmed that medication error and potential medication error will be reported in PSURs. In view of these measures, and the pharmacovigilance and risk minimisation activities already in place, the RMP evaluator considers that not including 'medication error' in the summary of safety concerns is acceptable.

- The sponsor has not responded to RMP evaluator's second round recommendations on measures to ensure patients will take blood testing before the start of each cycle. The RMP evaluator notes that it is anticipated some patients would undergo dose modification/interruption with additional monitoring. In view of this, measures to ensure that patients undergo blood testing before starting each cycle might not be critical. However, it can also be expected that some of the patients will have the full cycle of treatment without dose modification/interruption. While noting that information regarding blood testing is included in the PI, the RMP evaluator considers that alerting patients about the need for blood testing prior to start of a new cycle would be beneficial to the subset of patients who do not undergo additional monitoring during the treatment cycles.
- It is raised to the Delegate's consideration whether measures such as indicating in the pack insert leaflet that a blood test is required before each cycle and restricting prescribing/ dispensing (prescribing with no repeats or educating the patients that a blood test is necessary prior to starting a new cycle) are warranted in this context.

New and outstanding recommendations from second round evaluation

One unresolved issue remains at the end of the post-second round RMP evaluation. It is raised to the Delegate's attention as below.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement EU RMP (version 5, date 16 February 2017; data lock point 24 July 2015) with ASA (version 3.8, date 13 March 2017) and any future updates as a condition of registration.

Other advice to the Delegate

It is raised to the Delegate's consideration whether measures such as indicating in the pack insert leaflet that a blood test is required before each cycle and imposing restrictions on prescribing/dispensing are warranted in this context.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

According to the evaluator, there are outstanding issues with respect to labelling and clearance of GMP certification. It is hoped that these will be resolved prior to the ACM meeting.

The evaluator states that:

> *'Otherwise, registration is recommended with respect to chemistry, quality control and bioavailability aspects'.*

Of note, the Pharmaceutical Subcommittee (PSC) has reviewed various aspects of the submission on 2 separate occasions. A pharmacometric evaluation including replication of the analysis was considered at the 170th meeting of the PSC. While the results of the final population PK models for both FTD (trifluridine) and TPI (tipiracil) could be replicated, assessment of the report raised multiple questions in regard to the appropriateness of some model building techniques. These were communicated back to the sponsor. Following this, the PSC commented on the sponsor's response to each of the 21 issues.

The committee noted that CrCL is a significant covariate for oral clearance (CL/F). The committee questioned why dosing was not adjusted on CrCL in light of data on the incidence of increased toxicity with renal impairment. It was noted that the PI includes data on the pharmacokinetic/pharmacodynamic relationship. Importantly, that higher exposures and lower CrCL resulted in greater efficacy and also greater likelihood of Grade 3 or greater neutropaenia. There were no statistical analyses to demonstrate if the differences were significant.

The final recommendation of the committee is as follows:

> *'Overall the PSC were of the view that despite misinterpretation of some of the points raised by the evaluator, they were satisfied the sponsor had mostly addressed the concerns raised and there were no more outstanding population pharmacokinetic issues that would preclude registration of trifluridine / tipiracil HCl combination products.*
>
> *The PSC also advised that the proposed PI should be accepted with amendment to reflect dose modification with renal impairment.'*

Nonclinical

The nonclinical evaluation report was considered. There are no objections on nonclinical grounds to the proposed registration of Lonsurf.

The submitted dossier was compliant with the relevant ICH guideline on the development of anti-cancer pharmaceuticals. All pivotal toxicity studies were conducted under GLP conditions. The non-clinical evaluator states that the primary pharmacology studies support the use of FTD:TPI for the proposed indication. The main toxicities identified in repeat-dose studies were gastrointestinal, lymphatic and haematopoietic toxicity. Bone marrow suppression, infection and gastrointestinal effects were identified as safety concerns. Abnormalities of incisors observed in rats may also be applicable to the paediatric population.

Pregnancy Category D was recommended by the nonclinical evaluator.[11] This was accepted by the sponsor. The sponsor has also accepted the remaining recommendations from the nonclinical evaluator regarding the proposed PI documents.

Clinical

Clinical evaluator's view

The evaluator's view is that the benefit-risk balance of trifluridine and tipiracil in the proposed usage is favourable and the evaluator recommends that the application for registration of trifluridine and tipiracil be approved.

Overview of data

The clinical data package included one pivotal Phase III clinical study that addressed the safety and efficacy of trifluridine and tipiracil (Study TPU-TAS-102-301 (RECOURSE)). This study was supported by a Phase II clinical efficacy and safety study in Japanese patients. A total of 6 Phase I clinical pharmacology studies were presented that included pharmacodynamic and pharmacokinetic data, with 5 preliminary Phase I dose-finding studies (termed 'legacy studies'). The package also included one population pharmacokinetic analysis, an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS).

Formulation

A total of 14 clinical studies support the submission. Over the course of the studies, the tablet formulation of TAS-102 was stated to have been refined and improved. The Early Clinical Trial Material (CTM) Formulation was developed from the initial base with the aim on optimising the manufacturing method and replacing the disintegrant of carmellose with pre-gelatinised starch. The Early CTM Formulation was further modified to create the Late Clinical Trial Material (CTM) Formulation by: 1) the addition of ferric oxide as a colouring agent (coating suspension, 20 mg tablet only); 2) the addition of magnesium stearate; 3) the removal of ethanol from the coating suspension; 4) the change of the 20mg tablet shape from oval to round. The Late CTM Formulation represented a formulation suitable for use in large scale clinical trials.

According to the sponsor, the To-Be-Marketed Formulation tablets are identical to the late CTM Formulation tablets, with the exception of imprinting.

The sponsor has not submitted clinical studies comparing the in vivo bioequivalence of the Late CTM, the Early CTM and the TBM formulations. The clinical evaluator concluded that the similarity of the in vitro dissolution data for the relevant formulations support the sponsor's decision not to submit a clinical study comparing the TBM formulation to the Early and Late CTM formulations.

Pharmacology

A total of 12 clinical studies and 3 data analyses provided pharmacology data in patients with solid tumours. These included:

- 5 initial does-finding Phase I studies. As no patient received the proposed dose of TAS-102 (that is, 35mg/m^2 BD), these initial 5 Phase I studies were referred to as 'legacy studies'.
- 6 key clinical PK studies, summarised in Table 1 below.
- A population PK study (Study 12DA25), which pooled data for trifluridine (TFD) and tipiracil (TPI) obtained from dense sampling from 3 Phase I studies (Studies J001-10040010, TPU-TAS-102-102, TPU-TAS-102-103) and from sparse sampling from the pivotal Phase III Study TPU-TAS-102-301 (RECOURSE).
- An exploratory PK/PD report of data collected during the pivotal Phase III study (RECOURSE), submitted as part of the CHMP Day 120 List of Questions.
- An analysis of cardiac safety (Study TPU-TAS-102-103).
- An analysis of the correlation between haematologic toxicity and both the dosage and the pharmacokinetics of TAS-102 was presented in Study J001-10040010.
- A mass balance study (Study TPU-TAS-102-108).

Overall, the clinical evaluator concluded that the submitted data are considered to have adequately characterised the PK of FTD and TPI when administered as a fixed dose

combination tablet (TAS-102) at the proposed dose of 35 mg/m^2 BD (based on BSA) for the treatment of advanced mCRC. Key findings include:

- A relative bioavailability study was submitted in lieu of an absolute bioavailability study in humans. The sponsor submitted a justification for this decision which was accepted by the clinical evaluator. The sponsor also highlights that this approach is in accordance with the TGA guidance for a new chemical entity such as the fixed dose combination product trifluridine/tipiracil, where a relative bioavailability study is acceptable in the absence of an absolute bioavailability study. The clinical evaluator states that the results indicate that the absorption of TPI is not significantly different for tablet and oral solution formulations. The relative bioavailability for the FTD metabolites FTY and 5-CU were similar to that of the parent compound. Overall, the clinical evaluator concludes that the relative bioavailability data suggests that the fixed-dose TAS-102 combination tablet (late CTM formulation) containing FTD and TPI has been optimally formulated.
- The clinical evaluator notes that studies investigating the effect of TPI on the bioavailability of FTD support the rationale for a FDC product (FTD plus TPI) rather than FTD alone. In particular, the sponsor comments that simple extrapolation based on the AUC values indicates that the dose of FTD alone that would be necessary to achieve the FTD AUC observed after administration of TAS-102 is 1295 mg/m^2 (that is, 35 mg/m^2 x 37). The sponsor reported that this oral dose of FTD is predicted to exceed the projected lethal dose for humans of 1194 mg/m^2, based on primate toxicology studies. The equivalent dose in monkeys was reported to be associated with severe gastrointestinal and haematologic toxicities.
- The major limitations of the PK data relate to the absence of dedicated clinical studies assessing the effects of hepatic and renal impairment on the PK of TAS-102. Data from RECOURSE suggests that both mild and moderate renal impairment can increase exposure. However, the sponsor has indicated that such studies will be submitted to the EMA by the end of 2017.
- Data from Study J001-10040010 demonstrate that systemic exposure ($AUC_{0\text{-last}}$) to FTD increases more than dose proportionally over the TAS-102 dose range 15 to 35 mg/m^2/day, while exposure (C_{max} and AUC) to TPI is dose proportional over the dose range. Following multiple doses of TAS-102 (35 mg/m^2 BD), the $AUC_{0\text{-last}}$ of FTD accumulated approximately 3 fold on Day 12 compared to Day 1 and the C_{max} accumulated approximately 2 fold (Study TPU-TAS-102-102). However, there was no further accumulation of FTD in subsequent cycles. There was no accumulation of TPI following multiple doses of TAS-102. The mechanism for accumulation of FTD following multiple daily dosing has not been identified.
- The inter-subject variability of both FTD and TPI was high, with CV% values for $AUC_{0\text{-last}}$ and C_{max} being 60.9% and 64.3%, respectively, for FTD and 54.3% and 58.6%, respectively, for TPI.
- The intra-subject variability of both FTD and TPI was moderate to low, with CV% values for $AUC_{0\text{-last}}$ and C_{max} being 16.4% and 25.4%, respectively for FTD, and 28.9% and 36.0%, respectively, for TPI.
- The effect of food on the PK of FTD and TPI was investigated in the single dose crossover Study J004-10040040. The clinical evaluator concludes that this study showed that when compared to the fasting state, food significantly reduced the $AUC_{0\text{-inf}}$ and C_{max} values of TPI by 44% and 42%, respectively, and the C_{max} value of FTD by 39%. The significantly lower C_{max} values for FTD and TPI in the fed compared to the fasted state suggest that potential toxicities of TAS-102 might be reduced if the product is administered with food.

- No dedicated clinical drug-drug interaction studies were conducted. In the population PK analysis (Study 12DA25), OCT2 inhibitors did not demonstrate significant effects on TPI, despite the product undergoing renal tubular secretion. Concomitant administration of OCT2 inhibitors had no effect on the PK parameters of FTD. However, the clinical evaluator highlighted that these data should be interpreted cautiously as only 10% of the 239 patients in the dataset were receiving OCT2 inhibitors. In vitro studies with human biomaterials were reported to show that neither FTD nor TPI are metabolised by the broad range of CYP enzymes tested. In addition, FTD and FTY (main metabolite of FTD) were reported not to inhibit or induce the CYP enzymes tested. It was also reported that the in vitro data showed that TPI did not inhibit or induce the CYP enzymes tested. However, the European Union CHMP expressed its concern that that the maximum concentration of TPI used in the CYP induction studies was too low to definitively exclude TPI mediated induction of CYP enzymes. The sponsor has indicated that it will conduct an additional CYP study investigation induction at higher TPI concentrations.

The Delegate agrees with the clinical evaluator that PK has been adequately profiled in the submitted data. It is noted that additional data is required to investigate issues including TPI mediated induction of CYP enzymes and the effects of hepatic and renal impairment on the PK of TAS-102.

Efficacy

One pivotal efficacy study was submitted titled Study TPU-TAS-102-301(also known as RECOURSE). The sponsor also provided sensitivity and subgroup analysis, in addition to an updated efficacy analysis (submitted as part of the sponsor's Day 180 responses to the EMA's CHMP).

Study TPU-TAS-102-301(RECOURSE)

This was a randomised, double blind, Phase III study of TAS-102 plus best supportive care (experimental arm) versus placebo plus BSC (control arm) in patients with metastatic colorectal cancer refractory to standard chemotherapy. Of note, the inclusion criteria did not include patients who were refractory to regorafenib, since this medicine was not registered in participating countries at the start of enrolment. In Australia, regorafenib is approved for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy; AND patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

A total of 798 patients received treatment in the study (a total of 533 received TAS-102; and 265 received placebo) and 760 (95%) patients were evaluable for assessment of tumour response (TR Population). The overall median follow-up for all patients was 11.8 months.

In RECOURSE, randomised patients were stratified by KRAS status (wildtype versus mutant), time since diagnosis of metastasis (< 18 months versus ≥ 18 months), and geographic region (Region 1: Asia (Japan) versus Region 2 Western (Australia, Europe, US)). In the ITT population, the median age of the total population was 63 years, with 44% of the population being ≥ 65 years of age. Of the total patient population, 61% of patients were male, 58% were Caucasian/White and 35% were Asian/Oriental. All patients had a baseline ECOG performance status of 0 or 1. 51% of patients had tumours categorised by investigators as KRAS mutant, and 49% of patients had KRAS wild-type at study entry. The time since diagnosis of metastasis was ≥ 18 months for the majority of patients (79%). The 2 treatment arms were similar with respect to cancer diagnosis, including time from initial

diagnosis and randomisation and time from confirmed metastasis to randomisation. The 2 treatment arms were also comparable with respect to prior cancer therapies.

The primary efficacy end point analysis (analysis cut-off date 24 January 2014) showed a statistically significant, but modest increase in median OS of 1.8 months in the TAS-102 arm compared to the placebo arm (HR of 0.68 (0.58,0.81), p-value < 0.0001 (1 sided and 2 sided)). The Kaplan-Meier curves began to separate in favour of TAS-102 at approximately 2 months after randomisation, and separation was maintained throughout the course of the study. The percentage of patients surviving at 1 year was estimated to be 26.6% in the TAS-102 arm and 17.6% in the placebo arm.

A total of 3 covariate factors were identified as having a significant effect on OS (noted to be: time since diagnosis of first metastasis, ECOG performance status and number of metastatic sites). The magnitude of the TAS-102 treatment effect after adjusting for all 3 significant prognostic factors was maintained, indicating that the prognostic factors do not add to the effect seen for treatment alone. The multivariate model estimate for the HR for TAS-102 relative to placebo remained at 0.69 ((95% CI: 0.58, 0.81); p < 0.0001), which is consistent with the primary analysis of OS in the ITT population.

In general, the results for OS were consistent across other pre-specified subgroups including age (< 65 years, ≥65 years), race, gender, BRAF status, primary tumour site (colon, rectum), baseline ECOG score, number of prior regimens, number of metastatic sites (1 to 2; ≥ 3) and geographic subregion (Australia, Europe, US), with hazard ratios ranging from 0.49 to 0.75. For some parameters, such as BRAF status and race, the small sample sizes precluded any meaningful analyses. Among patients who had received only 2 prior regimens (n = 95, TAS-102; n = 45, placebo), the HR was 1.05; based on the Kaplan-Meier curves, a favourable risk reduction was evident throughout the follow-up period, but after 10 months the curves overlap and cross. The sponsor states that this finding is possibly due to the small sample available at that time, resulting in a confounded HR estimate.

The additional data supplied included an updated OS analysis based on a data cut-off of 8 October 2014. In this analysis, the median survival was 7.2 months (95% CI: 6.6, 7.8) in the TAS-102 arm and 5.2 months (95% CI: 4.6, 5.9) in the placebo arm, with a HR of 0.69 (95% CI: 0.59, 0.81), p < 0.0001 (1-sided and 2-sided), stratified log-rank test. The updated OS analysis was based on a total of 712 deaths in the ITT population compared to a total of 574 deaths in the ITT population in primary analysis. The OS results for the updated analysis were supportive of the primary OS analysis results.

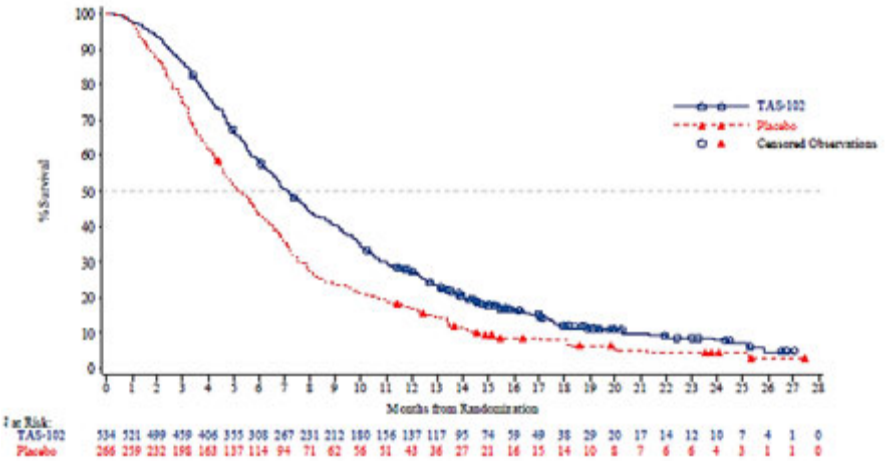
Table 7: OS, ITT population, updated data cut-off 8 October 2014

Parameter	TAS-102 (N = 534)		Placebo (N = 266)[e]	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (dead)	463 (86.7%)		249 (93.6%)	
Censored	71 (15.3%)		17 (6.4%)	
Survival (months)[a] (95% CI)[b]				
25th percentile	4.1	(3.8, 4.6)	3.0	(2.6, 3.3)
Median	7.2	(6.6, 7.8)	5.2	(4.6, 5.9)
75th percentile	12.5	(11.2, 13.6)	8.4	(7.5, 10.7)

Parameter	TAS-102 (N = 534)		Placebo (N = 266)[e]	
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. 2 patients randomised in the placebo group, initiated TAS-102 treatment (cross-over) after the study was unblinded in May 2014. For the ITT analysis presented in the above Table, both patients were still counted in the placebo group.

Figure 5: OS Kaplan-Meier curves, ITT population, updated data cut-off 8 October 2014



Study TPU-TAS-102-301 (RECOURSE); secondary efficacy endpoints

- 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 at the pre-specified cut-off date for non-survival data (31 January 2014). A median time of 2.0 months was found in the TAS-102 arm and 1.7 months in the placebo arm, resulting in a small difference of 0.3months (HR = 0.48 (95% CI: 0.41, 0.57), p < 0.0001 (1-sided and 2-sided), stratified log-rank test). The majority of PFS events in both treatment arms were investigator-assessed radiological disease progression, with such events being reported more frequently in the placebo arm than in the TAS-102 arm (85.0% versus 80.9%, respectively). The Kaplan-Meier curves began to separate in favour of the TAS-102 arm from 2 months after randomisation. The results of the supportive analyses of PFS were consistent with the results of the primary analysis, as were the results based on the stratification factors. The median PFS results for the subgroup analyses numerically favoured the TAS-102 arm compared to the placebo arm for all subgroups, apart from the Australian subpopulation.
- Time to treatment failure was defined as the time (in months) from the date of randomisation until the date of radiologic disease progression, permanent discontinuation of study treatment, or death due to any cause as of the pre-specified

cut-off date of 31 January 2014 for non-survival data. The median TTF was 1.9 months for the TAS-102 arm compared to 1.7 months for the placebo arm with HR of 0.50 (95% CI: 0.42, 0.58), p < 0.0001 (stratified log-rank test).

- Overall response rate (ORR) was based on investigator review of radiologic images and was restricted to patients with measurable disease (at least 1 target lesion) at Baseline and with at least one tumour evaluation while on study treatment (TR population). There was no statistically significant difference in ORR between the 2 treatment groups. Of note:
  - One patient in the placebo group achieved a CR. The sponsor states that the patient's target lesions at baseline were lymph nodes only and the sum of diameters was 30 mm, which decreased during treatment to 6 mm that qualified as CR according to RECIST (nodes that shrink to < 10 mm short axis are considered normal) (see Clinical Study Report for RECOURSE).
  - No patient in the TAS-102 group achieved a complete response; a total of 8 patients achieved a partial response (see Clinical Study Report for RECOURSE).
  - A statistically significant difference in favour of TAS-102 was seen in the disease control rate (DCR) between the 2 groups (44% in TAS-102 group compared to 16.3% in placebo group, p-value < 0.0001(Fisher's Exact test (2-sided)).
- In the pre-specified analysis of time to worsening ECOG PS status ≥ 2 in the ITT population, the median time to ECOG PS ≥ 2 was 5.7 months in the TAS-102 arm compared to 4.0 months in the placebo arm with HR of 0.66 (95% CI: 0.56, 0.78), p < 0.0001 (stratified log-rank test). Inspection of the Kaplan-Meier curves for time to ECOG performance status ≥ 2 showed that the curves began to separate in favour of the TAS-102 arm at about 2 months and remained separated throughout the remainder of the study.

Efficacy in special populations

A summary of the efficacy analyses in special populations can be found in the CER. In summary, median OS was longer in the TAS-102 group than in the placebo group for patients aged < 65 years, patients aged 65 to 74 years, male patients, female patients, Caucasian/White patients and Asian/Oriental patients.

Study J003-10040030

This was a placebo controlled, multicentre, double blind, randomised, Phase II study of TAS-102 in Japanese patients with unresectable advanced or recurrent colorectal cancer who have had 2 or more chemotherapy regimens and who are refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin. The study was designed to evaluate the efficacy and safety of TAS-102 administered at a dose of 70 mg/m^2 per day based on BSA, administered in 2 equal doses of 35 mg/m^2 within 1 hour of the morning and evening meals. Patients who met the eligibility criteria were randomised (2:1) to TAS-102 or placebo, with randomisation being stratified by ECOG performance status (PS = 0 versus PS = 1 or 2). Key findings include:

- The difference in median OS between the 2 treatment groups was 2.4 months in favour of the TAS-102 group.
- The median OS in the FAS was 9.0 months in the TAS-102 group and 6.6 months in the placebo group: HR=0.56 (95% CI: 0.39, 0.81); p = 0.0011, stratified log-rank test.
- The secondary efficacy endpoint of PFS assessed by an independent review committee demonstrated that median PFS was 2.0 months in the TAS-102 group compared with 1.0 month in the placebo group: HR=0.41 (95% CI: 0.28, 0.59); nominal p < 0.0001, stratified log-rank test.

- The results for the median TTF (secondary efficacy endpoint) assessed by the independent review committee was consistent with results for the PFS.
- For best tumour response assessed by independent review committee, the ORR (CR + PR) was negligible for both treatment groups (0.9% (1/112), TAS-102 versus 0% (0/57), placebo; nominal p = 1.000, Fisher's Exact test).
- The DCR (CR + PR + SD) assessed by independent review committee was 43.8% (49/112) in the TAS-102 group and 10.5% (6/57) in the placebo group (nominal p < 0.0001, Fisher's Exact test).
- No statistical adjustments were made for multiple pairwise testing of the secondary efficacy endpoints. The clinical evaluator concludes that the secondary efficacy endpoints should be considered to be exploratory rather than confirmatory, with all significant p-values being nominal.

Quality of life

There were no data in the RECOURSE study relating to patient or physician reported life-style outcomes. Although, the time to worsening of ECOG PS ≥ 2 was longer in the TAS-102 group compared with to the placebo group (5.7 versus 4.0 months, respectively), the significant rate of adverse events must also be considered. The sponsor states that the time to worsening of ECOG PS provides some evidence that TAS-102 might have a modest beneficial effect on quality of life.

Safety

The safety analyses considered by the evaluator includes safety data from the RECOURSE study, data from the supportive Study J003-10040030, an Integrated Summary of Safety (ISS) report and an update to the ISS submitted as part of the sponsor's Day 120 CHMP response. The ISS included a total of 4 Safety Data Groups.

The clinical evaluator emphasised the data from the pivotal RECOURSE study. The reasoning for this was that the RECOURSE study contributed the majority of data to Safety Data Groups 1 and 2, in addition to providing a relatively unbiased assessment of safety in the 2 treatment groups. The evaluator states that the safety of TAS-102 for the proposed indication has been satisfactorily characterised in the pivotal Phase III study. Overall, the clinical evaluator concludes that the risks of trifluridine/tipiracil (TAS-102), given the proposed usage, are considered to be favourable.

Study TPU-TAS-102-301 (RECOURSE)

Of the 800 patients with mCRC and randomised, 798 received at least one dose of study medication and were included in the safety population (referred to as the 'as treated' (AT) population). Of this group, a total of 533 patients received TAS-102 (mean of 12.7 weeks and median of 6.7 weeks of exposure) and a total of 265 patients received placebo (mean of 6.8 and median of 5.7 weeks of exposure). All safety summaries in RECOURSE were performed in the AT population. As of the data cut-off date (31 January 2014), the mean duration of treatment was twice as long for patients receiving TAS-102 as for patients receiving placebo (12.65 versus 6.76 weeks, respectively), while the total time on treatment was almost 4 times longer in the TAS-102 group compared to the placebo group (6744 versus 1791 weeks, respectively).

The data on patients who have been treated for longer than 6 months was limited, with a maximum of 6 x 28 day treatment cycles being initiated in only 37 (6.9%) patients in the TAS-102 group and 3 (1.1%) of patients in the placebo group. The clinical evaluator concludes that the small number of 28 day cycles initiated in both treatment groups, and the small number of patients for whom a maximum of 6 cycles were initiated reflects the

relatively poor prognosis of the patients with refractory mCRC included in the pivotal study.

Safety assessments included recording of AEs and SAEs from the time the patient signed the consent form through to 30 days after the last dose of study medication or until the initiation of new anticancer therapy.

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

In summary, the most common AEs in the TAS-102 group included the following:

- Gastrointestinal disorders including nausea, vomiting, diarrhoea, constipation and upper abdominal pain (77.5% in the TAS-102 group versus 60.8% in placebo).
  - Of note, nausea was the most common adverse event in the TAS-102 group AT population in the RECOURSE study at 48.4% (compared to 23.8% placebo).
- General disorders and administration site conditions; predominantly fatigue, pyrexia and asthenia (70% in the TAS-102 group versus 12.9% in placebo).
- Blood and lymphatic disorders associated with myelosuppression: predominantly anaemia, neutropaenia leukopaenia (57% in the TAS-102 group versus 10.9% in placebo).
  - Of note, anaemia was the second most common adverse event in the TAS-102 group AT population in the RECOURSE study at 40.2% (compared to 8.3% placebo).
- Investigations: predominantly neutrophil count decreased, white blood cell count decreased, and platelet count decreased (54.6% in the TAS-102 group versus 34.7% in placebo).
- Metabolism and nutrition disorders: (46.5% in the TAS-102 group versus 39.2% in placebo).
- Infections and infestations: (27% in the TAS-102 group versus 15.8% in placebo).

Treatment-related AEs (all grades) were reported notably more frequently in patients in the TAS-102 group than in the placebo group (85.7% versus 54.7%, respectively). Treatment-related AEs reported in ≥ 10% of patients in the TAS-102 group (versus placebo), in descending order of frequency, were nausea (39.4% versus 10.9%), anaemia (31.5% versus 4.5%), neutropaenia (28.7% versus 0%), neutrophil count decreased (27.2% versus 0.4%), decreased appetite (26.5% versus 11.3%), WBC decreased (26.3% versus 0.4%), fatigue (24.8% versus 10.2%), diarrhoea (23.6% versus 9.1%), vomiting (20.1% versus 4.5%), platelet count decreased (14.4% versus 1.5%), and asthenia (10.9% versus 4.5%).

In RECOURSE, although nearly all patients in both treatment groups experienced at least 1 AE, the majority of events were manageable by dose modifications rather than treatment discontinuation. A significant proportion of patients in the TAS-102 group experienced AE's resulting in interruption/delay or reduction of study medication. This was reported in 54.2% (n = 289) of patients in the TAS-102 group and 13.6% (n = 36) of patients in the placebo group. The majority of these events were characterised as Grade > 3 AEs. A much smaller proportion of patients experienced AE's leading to discontinuation of study treatment. Overall, a total of 10.3% of patients in the TAS-102 group discontinued

compared to 13.6% in the placebo group. However, a much smaller number indicated an adverse event/SAE as the primary reason for discontinuation (3.6% (n = 19) of patients in the TAS-102 group and 1.5% (n = 4) of patients in the placebo group). This discrepancy is explained by the sponsor as attributable to differences in the assessment of AE's of disease progression leading to discontinuation.

Adverse events and patient groups of special interest

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

- There was evidence that TAS-102 was associated with a small increased risk of renal related adverse events (predominantly proteinuria), however renal laboratory abnormalities associated with serum creatinine concentration did not significantly differ between the 2 treatment groups.
- Thromboembolic events were reported marginally more frequently in patients in the TAS-102 group compared to placebo, with the difference relating to the increased risk of pulmonary embolism.
- Haematological laboratory tests showed that Grade ≥ 3 abnormalities for leukopaenia, neutropaenia, lymphocytopaenia, anaemia, and thrombocytopaenia were reported more frequently in the TAS-102 group than in the placebo group. Clinical chemistry laboratory tests showed that Grade ≥ 3 abnormalities for hyperglycaemia occurred more frequently in patients in the TAS-102 group compared to the placebo groups, with Grade ≥ 3 abnormalities for other clinical chemistry parameters not notably differing between the 2 treatment groups.
- There was no evidence that TAS-102 was associated with an increased risk of cardiac disorders (ischaemia or arrhythmia). There were no notably differences between the 2 treatment groups in vital signs or in ECG changes relating to QTc prolongation. Patients in the TAS-102 group were not at an increased risk of hospitalisation compared to patients in the placebo group.
- There was no evidence that TAS-102 was associated with an increased risk of hepatobiliary related adverse events or hepatobiliary laboratory abnormalities (AST, ALT, bilirubin, SAP). Hy's law biochemical criteria for drug induced liver injury were reported in 3 patients in the TAS-102 group and 2 patients in the placebo group. However, for each of the 3 patients in the TAS-102 group the biochemical criteria were explained by hepatic conditions other than drug induced hepatic toxicity. The sponsor provided a dedicated hepatic impairment study submitted with the sponsor's response. Based on the results of this study, an additional statement is proposed in the PI under the section 'Pharmacokinetics in Special Populations (Hepatic impairment)'. The clinical evaluator recommends that this statement be amended to indicate that the number of patients with moderate hepatic impairment in the dedicated hepatic impairment study was too small to allow meaningful comparisons relating to exposure to be made in this patient population and patients with normal hepatic function. In addition, it is recommended that the statement notes that enrolment into the dedicated hepatic impairment study was discontinued due to the high incidence of Grade 3 or 4 increased bilirubin levels in patients with moderate hepatic impairment.

Post-market experience

Trifluridine/tipiracil (Lonsurf) was launched in Japan on 26 May 2015. There have been 205 serious adverse reactions (SARs) in 110 cases from Japanese post-marketing experience reported from 25 July 2014 until 24 July 2015. Of the 205 reported SARs,

39 events in 22 case reports were characterised as suspected unexpected serious adverse reactions (SUSARs). Of note:

- The 39 SUSAR events included 6 events of 'Febrile neutropaenia', 5 events of 'Disseminated intravascular coagulation', 4 events of 'Interstitial lung disease', 2 events of 'Pneumonia', 2 events of 'Bone marrow failure', 2 events of 'Cardiac failure congestive'.
- Of the 5 cases of 'Disseminated intravascular coagulation' reported during the collection period, 4 were considered to be possibly related to Lonsurf since these events were likely secondary to infection caused by chemotherapy induced bone-marrow suppression. The remaining case was assessed as 'Unassessable' at the time of data lock point.
- In a document titled 'Post-marketing experience in patients with unresectable advanced or recurrent colorectal cancer', the sponsor stated that 'To date, TAS-102 has been authorised for use in 2 countries, Japan (March 24, 2014) and USA (September 22, 2015). There have been reports of interstitial lung disease in patients receiving Lonsurf in post-approval use in Japan'. This statement appears in the draft PI document for Lonsurf and Orcantas.

Overall, the clinical evaluator concludes that the safety of TAS-102 for the proposed indication has been satisfactorily characterised in the pivotal Phase III study (RECOURSE). These data demonstrated that the safety profile of TAS-102 was inferior to the safety profile of placebo. The most frequently reported risks associated with TAS-102 were myelosuppression (anaemia, leukopaenia, neutropaenia, febrile neutropaenia and thrombocytopaenia), gastrointestinal events (nausea, vomiting and diarrhoea), and infections (predominantly nasopharyngitis, urinary tract infection, and upper respiratory tract infection). In general, the adverse events associated with TAS-102 were manageable by treatment interruption, delays in cycle initiation, and reductions in dose rather that by treatment discontinuation. The evaluator concludes that the safety results from the RECOURSE pivotal study were consistent with the safety results from the integrated safety data sets (Groups 1 and 2), and with the limited post-marketing safety experience reported in Japanese patients.

Risk management plan

Following second round evaluation, a total of 6 outstanding issues remain in relation to the Risk Management Plan (RMP) version 5.0 dated 3 November 2016 (data lock point 24 July 2015) and Australian Specific Annex (ASA) version 2, dated 8 December 2016. The outstanding issues are summarised below.

RMP outstanding issue 1

The RMP evaluator maintains that medication error should be included in the Summary of Safety Concerns. This recommendation was supported by the Advisory Committee on the Safety of Medicines (ACSOM) which reflected on the complexities of the dosing regimen (see ACSOM Meeting 36). In response to this recommendation, the sponsor maintains that medication errors are not considered to be an important potential risk but regardless of this, will be captured in the PBRER (see sponsor's Section 31 response). Furthermore, preventative measures (including packaging differentiation, prescribers and patients' guidances with PI, CMI and a MyLonsurf calendar) will be implemented to minimise the potential for medication errors. The RMP evaluator considers the dosing calendar and the pack insert leaflet are appropriate additional risk minimisation activities for medication error; however, maintains that this risk should be included in the Summary of Safety Concerns.

Delegate's comment

In the Delegate's opinion, the Delegate agrees with the RMP evaluator and the advice provided by the ACSOM. The Delegate acknowledges the sponsor's view and the Delegate supports the sponsor's implementation of additional risk reduction activities for the risk of medication error (including packaging differentiation, prescribers and patients' guidance with PI, CMI and a MyLonsurf calendar). The Delegate also agrees with the sponsor that medication errors will be included in Periodic Benefit-Risk Evaluation Report (PBRER); however, this may not capture medication errors that are not associated with an adverse outcome. Overall, it is the Delegate's opinion that the limited post-market experience with Lonsurf does not yet provide sufficient evidence that the suggested risk reduction measures are adequate for the risk of medication error with Lonsurf.

Recommendation to sponsor

Please include the risk of medication error as an important potential risk in the in the Summary of Safety Concerns.

RMP outstanding Issue 2

A new recommendation was introduced by the RMP evaluator following the sponsor's post-first round response. The RMP evaluator states: 'it is recommended to indicate in the pack insert leaflet that a blood test is required before the initiation of each cycle. The sponsor should clarify whether monthly prescribing and dispensing with no repeats on prescriptions will be carried out. If not, the sponsor should describe how it will ensure that blood counts are conducted before each cycle'.

Delegate's comment

The RMP evaluator raises an important issue regarding patient monitoring. However, some patients may require a different monitoring regime based on issues including adverse events, dose reduction and dose interruption. Therefore, patient monitoring is an important clinical practice issue and may not necessarily conform to the general statement of 'before the initiation of each cycle'. Although this information must be included in the PI for practitioners, it may lead to patient confusion if this was to be included in the pack insert.

RMP outstanding Issue 3

The sponsor states in the post first-round response that the dosing calendar and information sheet 'will be widely distributed to prescribers and pharmacies'. The sponsor should clarify the distribution method of these materials. While it is noted that the information leaflet is called the 'pack insert', the sponsor should clarify whether this leaflet will be inserted in every pack of tablets.

Question to sponsor

Please clarify the distribution method to prescribers and pharmacies and confirm if the information leaflet will be inserted into each pack of tablets.

RMP outstanding issue 4

The RMP evaluator noted the updates to the carton packaging, including improvements to the prominence of the strength of the tablets on the blister packs, the evaluator considers the difference between the 2 strengths of the tablets are not readily recognisable on the blister packs. Therefore, the RMP evaluator recommends that different colours are used on the blister packs for different strengths of the tablets. ACSOM also states that

'differentiation of the blister platforms by colour as well as text, in addition to different appearance of tablets' is recommended.

Delegate's comment

The Delegate agrees with the RMP evaluator and the ACSOM advice given. Clear differentiation of the blister packs when removed from their cartons is essential. The Delegate recommends differentiating with colour and/or tablet appearance.

Recommendation to sponsor

Please enhance the ability for patients to differentiate the strength of the tablets in the blister packs through differentiating with colour and/or tablet appearance. This is reasonable given the high likelihood that a patient's dose will vary in consecutive cycles due to toxicity and/or changes in BSA. Changes to the dose regime were seen in 54.2% of patients in the RECOURSE study. Patients must be able to adequately navigate these changes in the home setting.

RMP outstanding issue 5

The RMP evaluator and ACSOM recommend that a reference to materials including the dosing calendar should be included in the CMI.

Delegate's comment

The Delegate agrees that a reference to these materials would enhance the safety of the product.

Recommendation to sponsor

Please include a comment in the CMI that materials such as a dosing calendar are available to patients and advise on how patients can access these materials. If this comment will not be included in the CMI, please provide compelling justification for its exclusion.

RMP outstanding issue 6

A number of updates to the ASA have been recommended by the RMP evaluator. These include:

- During the next revision to ASA, risk minimisation section should be updated to show that a dosing calendar and a pack insert leaflet have been proposed as additional measures to mitigate the risk of medication error.
- The ASA section 'Pharmacovigilance activities for safety concerns specific to Australia' includes details about MyLonsurf Calendar and Pack insert leaflet. These are risk minimisation activities and not pharmacovigilance activities. Therefore, during the next ASA update, these details should be removed from this section and replaced with pharmacovigilance activities specific to Australia (if any).
- The details included in the ASA, 'How risk minimisation activities will be evaluated in Australia' are not relevant to how risk minimisation activities will be evaluated. Therefore, during the next ASA update, these details should be replaced with how the efficacy of additional risk minimisations activities will be measured using process indicators and/or outcome indicators.

Recommendation to sponsor

Please provide confirmation that the above changes to the ASA will be implemented during the next ASA update.

Recommended conditions of registration

The RMP evaluator states that suggested wording will be provided once the above issues have been addressed to the satisfaction of TGA.

Risk-benefit analysis

Delegate's considerations

Efficacy

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

The standard prior chemotherapy regimens used in the clinical studies are similar to regimens likely to be used in Australia for the treatment of mCRC. However, regorafenib, which is approved in Australia for a similar patient population studied in the pivotal and supportive studies, was not approved in any jurisdiction when the TAS-102 studies were designed. Consequently, there are limited data in the submission on patients previously treated with regorafenib. The OS subgroup analyses from the RECOURSE study showed that there was trend towards longer median survival time in patients in the TAS-102 arm compared to the placebo arm, irrespective of whether or not they had received prior treatment with regorafenib.

In the pivotal study (RECOURSE), the median OS was 7.1 months in the TAS-102 arm and 5.3 months in the placebo arm. The modest increase in OS of 1.8 months in the TAS-102 arm compared to the placebo arm was statistically significant: HR = 0.68 (95% CI: 0.58, 0.81), $p < 0.0001$ (1 sided and 2 sided), stratified log-rank test. The primary analysis of OS was supported by a number of additional OS analyses, including sensitivity analyses, analyses based on the individual stratification factors and subgroup analyses. The updated OS analysis (as of data cut-off date of 8 October 2014) was based on 712 deaths (463 (86.7%), TAS-102; 249 (93.6%), placebo). In the updated analysis, the median OS was 7.2 months in the TAS-102 arm and 5.2 months in the placebo arm: HR = 0.69 (95% CI: 0.59, 0.81); $p < 0.0001$ (1 and 2 sided), stratified log-rank test. The results of the updated OS analysis were supportive of the results for the primary OS analysis. The key secondary efficacy endpoint of PFS demonstrated a modest but statistically significant increase in medial PFS of 0.3 months in the TAS-102 arm compared to the placebo arm. The other secondary efficacy endpoints of TTF (ITT population), ORR, and time to ECOG status ≥ 2 all favoured the TAS-102 arm compared to the placebo arm with p-values being statistically significant.

As highlighted by the clinical evaluator, the modest improvement in OS and secondary efficacy endpoints in the TAS-102 arm compared to the placebo arm needs to be interpreted in the context of heavily pre-treated patients with mCRC resistant to standard treatments.

It is important to note that the pivotal study included only patients with ECOG PS 0 or 1 (56.0% versus 44.0%, respectively), and excluded patients with ECOG PS ≥ 2 (that is, patients with more severe impairment in quality of life due to mCRC). The Delegate agrees with the clinical evaluator that the absence of patients with ECOG PS ≥ 2 is considered to be a deficiency in the data. It can be anticipated that in clinical practice, a considerable

proportion of patients with refractory mCRC likely to be offered treatment with TAS-102 might be categorised with ECOG PS status ≥ 2.

Overall, it is my opinion that the efficacy of TAS-102 for the proposed indication has been demonstrated in the context of heavily pre-treated patients with mCRC resistant to standard treatments. However, it must be acknowledged that efficacy outcomes were modest in the pivotal and supportive study, in addition to known limitations of the data presented (including lack of data in patients with ECOG PS ≥ 2 and limited data in patients previously treated with regorafenib).

Question 1 for ACM

> What is the committee's opinion of the median 1.8 month increase in overall survival with TAS-102?

Safety

Although the AEs associated with trifluridine/tipiracil are consistent with a medicine containing an antineoplastic thymidine-based nucleoside analogue which interferes with DNA synthesis and inhibits cell proliferation, the rates of adverse events in the TAS-102 treatment group were significant. The incidence of treatment-related AEs was notably higher in the TAS-102 group than in the placebo group, as was the incidence of Grade ≥ 3 AEs and treatment-related SAEs. In the context of the short duration of exposure documented in the clinical dossier (reflecting the poor prognosis of patients included in the pivotal study), the most frequently reported risks associated with TAS-102 were myelosuppression, gastrointestinal events and infections. Fatal AEs occurred uncommonly in patients in the TAS-102 group and were more frequent in patients in the placebo group. There was an increased risk of AE's in certain groups of patients. This includes female patients, patients aged > 65 years of age and patients with renal impairment (particularly moderate renal impairment). Patients aged > 65 years of age had a higher incidence of anaemia, Grade 3 or 4 neutropaenia, thrombocytopaenia, leukopaenia and decreased appetite.

In the pivotal study (the RECOURSE study) although nearly all patients in both treatment groups experienced at least 1 AE, the majority of events were manageable by dose modifications rather than treatment discontinuation.

The risk of medication error is an important consideration given the complexity of the dose form and dosing regimen. Recommendations have been made to the PI to further address this risk. The sponsor has also implemented risk minimisation activities; however, some issues remain outstanding in regard to the risk of medication error (see RMP discussion below).

The Delegate agrees with the clinical evaluator that the submitted data provides comprehensive information regarding the safety profile of TAS-102. Recommendations have been made to ensure that the risks of Lonsurf/Orcantas are adequately communicated to prescribers, thereby assisting physicians to assess the risk/benefit profile for individual patients.

Question 2 for ACM

> Does the ACM consider that the safety of Lonsurf/Orcantas in the proposed use is sufficiently well characterised and communicated in the PI?

Planned or ongoing studies

According to the RMP version 5.0 dated 3 November 2016 (DLP 24 July 2015), 2 clinical studies are ongoing:

- A Phase I, open label study (Study TO-TAS-102-106): To evaluate the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours

and varying degrees of hepatic impairment. Planned submission of final report December 2017.

- A Phase I, open label study (Study TO-TAS-102-107): To evaluate the safety, tolerability, and pharmacokinetics of TAS-102 in patients with advanced solid tumours and varying degrees of renal impairment. Planned submission of final report December 2017.

Overall risk-benefit and indication

Balanced against the modest benefit in OS, there was a high incidence of severe and serious adverse reactions which warrant close monitoring. In particular, the risks of myelosuppression, gastrointestinal events and infections were prominent in the clinical trials. The majority of adverse events associated with TAS-102 were generally manageable by dose interruption, delay or reduction rather than treatment discontinuation. In the proposed indication of Lonsurf/Orcantas, the magnitude of the OS benefit is likely to outweigh the significant toxicity of the drug for some patients. It is also important to note that the potential impact on quality of life (QoL) is largely unknown, with only indirect measures of QoL currently available. The proposed use appears to have a positive benefit/risk balance, but the ACM's advice on this issue is requested.

The current proposed indication is:

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

It is the Delegate's preliminary view that the phrase 'available therapies' in the proposed indication may seek a broader indication than the clinical trial population. The Delegate would appreciate the committee's advice on this.

Question 3 for ACM

> Is the committee satisfied with the phrase 'available therapies' in the proposed indication?

The pivotal study was based on patients who had received at least 2 prior regimens of standard chemotherapies for mCRC and were refractory to or failing those chemotherapies. Standard chemotherapies must have included all of the following agents approved in each country: fluoropyrimidines, irinotecan and oxaliplatin; an anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab); and at least one of the anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab or panitumumab) for KRAS wild-type patients.

Question 4 for ACM

> What is the committee's opinion of the risk-benefit balance of trifluridine/tipiracil in the proposed indication?

Summary of issues

Please note the trifluridine/tipiracil tablets (proposed trade names of Lonsurf and Orcantas) will be referred to as 'TAS-102' in this overview.

- Clinical significance of efficacy outcomes.
- Risk of medication error.
- Appropriateness of the proposed indication.

- Risk-benefit balance.
- Multiple evaluation RMP issues outstanding at the time of writing this overview

Proposed action

It is the Delegate's preliminary view that the application for trifluridine/tipiracil should be approved for registration; however, this is subject to the advice received from the ACM.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. What is the Committee's opinion of the median 1.8 month increase in overall survival with TAS-102?
2. Does the ACM consider that the safety of Lonsurf/Orcantas in the proposed use is sufficiently well characterised and communicated in the PI?
3. Is the committee satisfied with the phrase 'available therapies' in the proposed indication?
4. What is the committee's opinion of the risk-benefit balance of trifluridine/tipiracil in the proposed indication?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

The sponsor welcomes the Delegate's recommendation the application for the new fixed dose combination product containing trifluridine/tipiracil should be approved for registration, subject to advice received from the ACM, for the following indication:

> *'Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents'.*
>
> *(Note: The sponsor proposes to remove 'available therapies including' from the proposed indication; see below)*

Advice sought by Delegate

In the Overview, the Delegate sought advice from the ACM on the following specific issues:

1. Clinical significance of efficacy outcomes.
2. Characterisation and communication of the safety of TAS-102 in the PI.
3. Appropriateness of the proposed indication.
4. Risk-benefit balance of TAS-102 in the proposed indication.

Clinical significance of efficacy outcomes

> *Delegate's Question to ACM: 'What is the Committee's opinion of the median 1.8 month increase in overall survival with TAS-102?'*

The sponsor notes the Delegate's confirmation the efficacy of TAS-102 has been demonstrated in the context of heavily pre-treated patients with mCRC refractory to at least 2 lines of standard chemotherapeutic regimen for the proposed indication:

> *'Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents'.*
>
> *(Note: The sponsor proposes to remove 'available therapies including' from the proposed indication (see below)).*

The sponsor agrees with the clinical evaluator that the increase in median OS observed for patients treated with TAS-102 represents a clinically meaningful and statistically significant survival benefit, especially in the context of heavily pre-treated patients with refractory mCRC.

An increase in median OS from 1.8 months for TAS-102 in the primary analysis (based on a data cut-off date of 24 January 2014) to a median OS of 2.0 months was observed in the updated analysis provided with the response to the first round evaluation report. Details of the updated OS analysis based on a cut-off date of 8 October 2014 were included in the PI at the request of the clinical evaluator. The updated OS analysis, carried out at 89% (n = 712) of events, showed an increase in median OS of 2.0 months following treatment with TAS-102, the median OS being 7.2 months in the TAS-102 plus BSC arm versus 5.2 months in the placebo plus the BSC arm (HR: 0.69; 95% CI (0.59 to 0.81); $p < 0.0001$), with 1 year survival Kaplan-Meier estimates of 27.1% and 16.6%, respectively.

This benefit of TAS-102 on the overall survival is associated with a good tolerance of the treatment, and a maintained physical condition for most of patients. The safety profile of Lonsurf is acceptable and manageable particularly when considering the advanced refractory nature of the disease and the safety profile of other chemotherapies used at this stage. Lonsurf was well tolerated by patients as indicated by the low frequency of AEs resulting in treatment discontinuation and dose reduction, and the evidence of the absence of an increased risk of hospitalisation with Lonsurf. Moreover, the general condition of the patients after treatment with TAS-102, as assessed by the physical status (according to the ECOG) was maintained for most of patients (64%). This maintenance of a relatively good condition of the patients after treatment with TAS-102 allows the possibility of further lines of chemotherapies.

In many patients, the additional survival time will be considered very valuable, particularly in patients who have tasks they want to accomplish before they die, for example, get their personal and financial affairs in order, share meaningful goodbyes and create memories with family and friends, pass along rich legacies of memories and wisdom, tick items off their 'bucket list'.

In summary, the relative improvement in overall survival is clinically relevant, as demonstrated by:

- a 38% improvement in median OS (increased from 5.2 months to 7.2 months);
- a 31% reduction in risk of death (HR: 0.69; 95% CI: 0.59 to 0.81); and
- a 63% increase in proportion of patients alive at 12 months (27.1% versus 16.6% for TAS-102- and placebo-treated patients).

Characterisation and communication of the safety of TAS-102 in the PI

> *Delegate's Question to ACM: 'Does the ACM consider that the safety of TAS-102 in the proposed use is sufficiently well characterised and communicated in the PI?'*

The sponsor welcomes the Delegate's agreement with the clinical evaluator that the submitted data provides comprehensive information regarding the safety profile of TAS-102. Although nearly all patients in both treatment groups in the pivotal study

(RECOURSE) experienced at least one AE, the majority of events were manageable by dose interruption, delay or reduction rather than treatment discontinuation.

Myelosuppression was the main AE caused by TAS-102 but was generally manageable with dose reductions or by delaying commencement of the next cycle of treatment. Febrile neutropaenia was reported in only 3.8% of patients administered TAS-102 in the RECOURSE trial. The safety profile of TAS-102 is distinct from that of fluoropyrimidines such as hand-foot-syndrome usually reported with fluoropyrimidines was reported with low frequency (2.3%) compared to capecitabine (>10%).[17]

Changes to the PI recommended by the Delegate to ensure that the risks of TAS-102 are adequately communicated to prescribers have been accepted and implemented, including a specific amendment recommending that TAS-102 not be used to treat patients with moderate or severe hepatic impairment. A summary table of all recommended changes to the PI is provided.

Appropriateness of the proposed indication

> *Delegate's Question to ACM: 'Is the committee satisfied with the phrase 'available therapies' in the proposed indication?'*

The sponsor welcomes the recommendations of the clinical evaluator and Delegate that TAS-102 be approved and, noting the Delegate's question to the ACM, proposes to remove 'available therapies including' from the indication statement:

> *'Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for~~, available therapies including~~ fluoropyrimidine-, oxaliplatin and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents'.*

Risk-benefit balance of TAS-102 in the proposed indication

> *Delegate's Question to ACM: 'What is the committee's opinion of the risk-benefit balance of Trifluridine/Tipiracil in the proposed indication?'*

The sponsor welcomes the Delegate's comment that TAS-102 appears to have a positive benefit/risk balance and agrees with the clinical evaluator the magnitude of the OS benefit represents a clinically meaningful (and statistically significant) survival benefit that is likely to outweigh the clinically-manageable toxicity profile of the drug.

RMP

The Overview identified the following 5 outstanding issues in relation to the RMP and ASA.

RMP issue 1: Risk of medication error

> *Delegate's recommendation: 'Please include the risk of medication error as an important potential risk in the Summary of Safety Concerns.'*

Medication errors (ME)[18] are an important cause of morbidity and mortality and many could be prevented or mitigated. However, this risk is not considered by the sponsor as an 'important potential risk' for the purpose of the RMP[19] as ME (associated or not with

[17] Australian PI of XELODA (capecitabine).
[18] According to the GVP, Module V : For the purposes of the RMP, medication error refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional or patient.
[19] According to the GVP, Module V.B.1. Terminology, an important risk is defined as 'an identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.'

adverse outcomes) are already closely monitored and, during the 3 first years of marketing no relevant findings were identified from the 198 cases reported (27,774 estimated patients exposed). Preventive measures to avoid ME have been considered and are proposed for Australia. These risk minimisation measures seem appropriate to better assist patients to differentiate between the 2 tablet strengths and to understand and adhere to their personalised dosing schedule.

In line with the TGA adopted EU Guideline on Good Pharmacovigilance Practices (GVP),[20] Marketing Authorisation Holders have: (a) to record, report and assess ME and potential ME[21] associated or not with adverse outcomes in their pharmacovigilance database and analysed them in the PBRER, (b) to reflect the current knowledge about the risk of ME in RMP for the purpose of continuous benefit-risk evaluation of medicinal products.

The first PBRER for trifluridine-tipiracil (period of 25 April 2016 to 25 October 2016, provided with this response) summarises relevant information on patterns of ME and potential ME, even when not associated with adverse outcomes. Since the first marketing authorisation (24 March 2014 in Japan; approved in 2015 in US and 2016 in EU), the estimated cumulative exposure to trifluridine-tipiracil is 27,774 patients (Post-marketing and Compassionate Use Program) with 198 ME having been reported in 188 patients treated with trifluridine-tipiracil.[22] Among them, 40 patients (21%) did not report any adverse events and 21 patients (14%) reported a serious event in the context of ME. The most frequently reported ME with a serious adverse event were 'Inappropriate schedule of drug administration' (9 patients) and 'Drug dose omission' (4 patients). The reported serious adverse events were in majority listed (nausea, fatigue, neutropaenia, anaemia) and unlisted events did not raise safety concerns. After analyses of all ME or potential ME in the first PBRER no relevant findings were identified from this analysis during the reporting period. An updated analysis will be performed in the second PBRER (26 October 2016 to 25 April 2017) including the new EU templates for summary tabulation and listing of individual cases of medication errors.[23]

According to Good Practice Guide on risk minimisation and prevention of ME,[24] Marketing Authorisation Holders should consider routinely the likelihood of ME (i), minimise the risk of ME (ii) and where medication errors result in adverse outcomes, corrective actions should be taken (iii).

- As required by GVP, ME should be discussed in the RMP in module SVI as 'additional EU requirements for the safety specifications'. The potential for ME with Lonsurf is assessed in the EU RMP module SVI.4 section, in particular with the description of ME reported during the clinical trial programme.
- In order to minimise the potential for ME, preventive measures were taken globally (invented name, packaging, dosing schedule detailed in SmPC and PIL) and additional specific Australian measures (packaging differentiation, prescriber and patient guidance present in the PI, CMI and MyLonsurf dosing calendar) will be implemented.
- If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of ME, this topic should be discussed in the updated RMP and ways of limiting the errors proposed, for example, ME should be included as a 'safety

[20] GVP, Module VII Periodic safety update report (Rev 1) and GVP, Module V Risk management systems (Rev 1).
[21] According to GVP Module VII.B.5.9 a potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient.
[22] Table (9.2.1) 1 - Medication errors cases reported since MA (Health Care Professional (HCP) and non-HCP cases), First Periodic Benefit-Risk Evaluation Report for TAS-102 (Period covered: 25 April 2016 to 25 October 2016), Date of report: 28 December 2016.
[23] As per Annex 2 in EMA: Good practice guide on recording, coding, reporting and assessment of medication errors, EMA/762563/2014, October 2015.
[24] Good practice guide on risk minimisation and prevention of medication errors, EMA/606103/2014.

concern' (that is, as an 'important identified risk', 'important potential risk' or 'missing information') with corresponding completion of the relevant RMP sections and with additional Pharmacovigilance activities to be proposed.

To date, no relevant findings were identified from the analysis performed for the first PBRER: ME is not considered as an 'important potential risk' for the purpose of the RMP of TAS-102.

RMP issue 2: Distribution of the dosing calendar and information sheet

> *Delegate's Question: 'Please clarify the distribution method to prescribers and pharmacies and confirm if the information leaflet will be inserted into each pack of tablets.'*

In addition to the MyLonsurf dosing calendar (a double-sided handout including a dosing calendar and information sheet) being provided to oncologists as a tear-off pad, it will also be available directly from the sponsor to oncologists and pharmacists. Confirmation is provided the pack insert (describing key information about TAS-102 including tablet description, dosing, treatment cycle and tips for administration, the MyLonsurf dosing calendar and instructions on how to source the CMI document) will be inserted into each pack of tablets.

RMP issue 3: Differentiation of the tablet strengths on the on the blister packs

> *Delegate's Recommendation: 'Please enhance the ability for patients to differentiate the strength of the tablets in the blister packs through differentiating with colour and/or tablet appearance…'*

The sponsor notes the comments of the Delegate and RMP evaluator in relation to the need for clear differentiation of the 2 different strength tablets. In addition to a number of additional measures already implemented, the sponsor proposes to use different coloured text on the foil for one of the strengths (Lonsurf 20/8.19; Orcantas 20/8.19) to further aid clear differentiation of the 2 different strength tablets. The existing black text on the blister foil for these 2 strengths will be replaced with text in the corresponding colour used on the carton. Updated blister foil mock-ups for Lonsurf 20/8.19 Orcantas 20/8.19 are provided with this pre-ACM response.

RMP 4: Reference to patient information materials in the CMI

> *Delegate's Recommendation: 'Please include a comment in the CMI that materials such as a dosing calendar are available to patients and advise on how patients can access these materials'.*

The CMI document has been updated to include reference to the availability of the MyLonsurf dosing calendar. The updated CMI document is provided with this pre-ACM response.

RMP 5: Updates to the ASA

> *Delegate's Recommendation 'Please provide confirmation that the above changes to the ASA will be implemented during the next ASA update.'*

The updates recommended by the RMP evaluator have been implemented in the latest version of the ASA (version 3.6, dated 13 March 2017) provided with this pre-ACM response.

Other issues raised by Delegate

Data in patients treated with regorafenib

The final clinical evaluation report noted a limitation of the pivotal study (RECOURSE) was the small amount of data in patients treated with regorafenib (Stivarga). While only 18.0% (n = 144) of the total number of patients in the RECOURSE ITT population had previously

been treated with regorafenib (17.0% (n = 91) TAS- 102; 19.9% (n = 53) placebo), reassuringly the OS subgroup analyses showed there was trend towards longer median survival time in patients in the TAS-102 arm, irrespective of whether or not they had received prior treatment with regorafenib. The Delegate's comment relating to single-agent use of regorafenib occurring overseas for patients with refractory mCRC who have been previously treated with standard chemotherapy is noted. However, local expert opinion sought by the sponsor confirms use of regorafenib in local clinical practice for the treatment of mCRC is negligible due to the unfavourable safety profile and high cost (regorafenib is not listed on the PBS).

Multiple evaluation and RMP issues outstanding at the time of writing the overview

The sponsor acknowledges the multiple evaluation (quality, nonclinical, clinical) issues outstanding at the time of writing of the Delegate's Overview. Notwithstanding the provision of the final evaluation reports on the same day as the Delegate's Overview, the sponsor believes all of the outstanding nonclinical, clinical and RMP issues have been appropriately addressed in this response and the additional documents provided below.

Outstanding issues; GMP clearance and sponsor details on carton

The Delegate noted a number of details remain outstanding, specifically:

- GMP clearance for the overseas manufacturers.
- Clarity of sponsor details on the carton labels.

The sponsor acknowledges GMP clearance for all sites must be finalised prior to approval and subsequent registration on the ARTG. Liaison with the TGA's Manufacturing Quality Branch is ongoing and it is hoped all outstanding GMP clearances will be obtained in the near future.

In response to the evaluator commenting the inclusion of the name of the Japanese licensor/manufacturer was confusing, the carton labels have been amended to more clearly identify the Australian sponsor details as follows:

- Increasing the prominence of the Australia sponsor details
- Inclusion of the text: 'Distributed In Australia by' immediately preceding the Australia sponsor details
- Inclusion of the text: 'Under Licence from' immediately preceding the reduced-prominence Japanese licensor/manufacturer) details

Copies of the updated carton labels are provided.

Advisory Committee Considerations[25]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Lonsurf and Orcantas fixed dose combination tablets containing 15 mg/6.14 mg trifluridine/tipiracil and 20 mg/8.19 mg trifluridine/tipiracil to have an overall positive benefit-risk profile for the amended indication:

[25] ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia, including issues relating to pre- and post-market functions for medicines. ACM is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. ACM was established in January 2017 replacing the Advisory Committee on Prescription Medicines (ACPM), which was formed in January 2010. ACM encompasses pre- and post-market advice for medicines following the consolidation of the previous functions of the ACPM, the Advisory Committee on the Safety of Medicines (ACSOM), and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

'Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.'

In making this recommendation, ACM:

- Advised that the indication, or the precautions in the PI, should specify that the medicine is only for use in patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Proposed conditions of registration

ACM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

ACM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

ACM advised the following in response to the Delegate's specific questions on the submission:

1. *What is the Committee's opinion of the median 1.8 month increase in overall survival with TAS-102?*

The ACM noted that while the survival increase of 1.8 months is modest, it is not insubstantial for this highly selected subgroup of patients who have exhausted other treatment options for their disease. The poor prognosis in this patient group is evidenced by the patients receiving placebo and BSC surviving a median 5.3 months. The adverse reaction profile is similar to medicines which patients would have already received as part of their prior treatments.

2. *Does the ACM consider that the safety of Lonsurf/Orcantas in the proposed use is sufficiently well characterised and communicated in the PI?*

The ACM advised that the PI appropriately addressed the toxicity issues. The amendments to the 'hepatic impairment' section in the pre-ACM PI were sufficient, noting that hepatic metastasis is a common complication of mCRC. The PI should state that the prescriber should be a specialist in the treatment of CRC.

3. *Is the committee satisfied with the phrase 'available therapies' in the proposed indication?*

The ACM advised that the phrase 'available therapies including' is too broad and should be deleted; the named therapies in the amended indication are consistent with the patient selection criteria used in the pivotal RECOURSE trial. 'Available therapies' could include unapproved clinical trial medicines or radiotherapy. In CRC, treatment therapies are used in various orders and may be reused after an intervening therapy.

4. *What is the committee's opinion of the risk-benefit balance of trifluridine/tipiracil in the proposed indication?*

ACM advised that the risk-benefit balance is favourable. Increased survival (by 1.8 months) and delayed time to deterioration in ECOG were balanced against the risks of AEs. There is no data supporting use in patient with ECOG performance status worse than 1.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lonsurf and Orcantas 15/6.14 trifluridine 15 mg/tipiracil hydrochloride 7.065 mg (equivalent to tipiracil 6.14 mg) and Lonsurf and Orcantas 20/8.19 trifluridine 20 mg/tipiracil hydrochloride 9.420 mg (equivalent to tipiracil 8.19 mg), film coated tablets indicated for:

> *'Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.'*

Specific conditions of registration applying to these goods

- The trifluridine/tipiracil EU-RMP, version 5, dated 16 February 2017; data lock point 24 July 2015) with ASA (version 3.8, dated 13 March 2017), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Lonsurf and Orcantas approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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