EU Risk Management Plan for Lonsurf
(Trifluridine (FTD) and Tipiracil hydrochloride (TPI))

RMP version to be assessed as part of this application

RMP version number: 11.0
Data lock point for this RMP: 24 September 2022
Date of final sign off: 07 March 2024

Rationale for submitting an updated RMP :

The RMP version 11.0 is submitted in the frame of the Type IB C.I.11.z to change the final due date of the study report for DIM-95005-001 (PROMETCO), a non-interventional real world data study, as an additional pharmacovigilance activity (category 3 study) that might further characterise the missing information "Use in patients in worse condition than ECOG 0-1".

Summary of significant changes in this RMP :

Postponement of the final due date of the study report for DIM-95005-001 (PROMETCO) from September 2024 to December 2024.

Details of the currently approved RMP:

Version number: 10.0

Approved with procedure: Type II variation EMEA/H/C/003897/II/0026

Date of approval (opinion date): 26 July 2023

QPPV name**: Dr. Fairouz SMAIL-AOUDIA**
QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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Abbreviations table

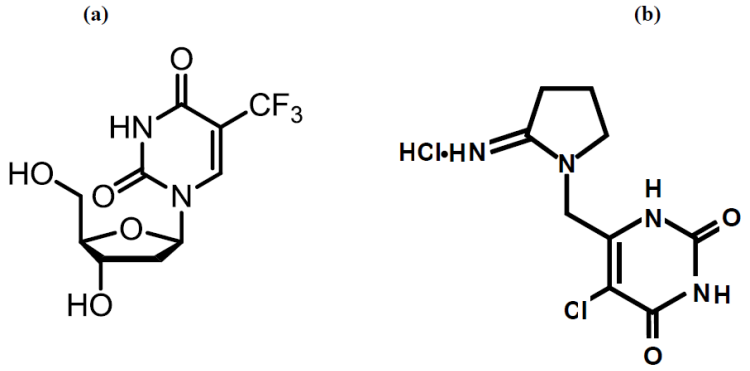
Abbreviation	Term
5-FU	5-Fluoruracil
Aes	Adverse Events
APC	Adenomatous Polyposis Coli
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AZT	Azidothymidine
BSA	Body Surface Area
BSC	Best Supportive Care
bid	bis in die (twice daily)
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Concentration
CRC	Colorectal Cancer
CLcr	Creatinine Clearance
CL/F	Oral clearance
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP	Cytochrome P450
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
dThd	Deoxythymidine
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAP	Familial Adenomatous Polyposis
FOLFIRI	Folinic Acid (FOL) Fluorouracil (5-FU) Irinotecan (IRI)

FOLFOX	Folinic Acid (FOL) Fluorouracil (5-FU) Oxaliplatin (OX)
FOLFOXIRI	Folinic Acid (FOL) Fluorouracil (5-FU) Oxaliplatin (OX) Irinotecan (IRI)
FTD	Trifluridine
G-CSF	Granulocyte Colony Stimulating Factor
GC	Gastric Cancer
GI	Gastrointestinal
HCT	Human Colon Cancer
HNPCC	Hereditary Non-Polyposis Colorectal Cancer
hERG	human Ether-a-go-go-Related Gene
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
kg	kilogram
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
m	meter
mCRC	metastatic Colorectal Cancer
mGC	metastatic Gastric Cancer
mg	milligram
min	minute
ml	milliliter
MLH1	mutL Homolog 1
msec	millisecond
MSH2	mutS Homolog 2
MUTYH	mutY Homolog
OCT	Organic Cation Transporter
OS	Overall Survival
PDCO	Paediatric Committee in the European Medicines Agency
PL	Patient Leaflet
PPD	Protected Personal Data
PK	Pharmacokinetics
PS	Performance Status
qd	quaque die (once a day)
QPPV	Qualified Person for Pharmacovigilance
RECOURSE	Refractory Colorectal Cancer Study (TPU-TAS-102-301 Phase 3 study)

RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STK1	Serin/Threonine Kinase 1
SUNLIGHT	Refractory Colorectal Cancer Study in combination with bevacizumab (CL3-95005-007 phase 3 study)
TAGS	TAS-102 Gastric Study (TO-TAS-102-302 Phase 3 study)
tid	ter in die (three times a day)
TNM	Tumour, Nodes, Metastases, (Classification of Malignant Tumours)
Tpase	Thymidine Phosphorylase
TPI	Tipiracil hydrochloride
US	United States
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substances (INN or common name)	Trifluridine (FTD) Tipiracil hydrochloride (TPI)
Pharmacotherapeutic group (ATC Code)	ATC code : L01BC59 trifluridine, combinations
Marketing Authorisation Holder	Les Laboratoires Servier
Medicinal products to which this RMP refers	Lonsurf 15 mg/6.14 mg film-coated tablets Lonsurf 20 mg/8.19 mg film-coated tablets
Invented name in the European Economic Area (EEA)	Lonsurf ®
Marketing authorisation procedure	Centralised
Brief description of the product	<u>Chemical class</u> Lonsurf (also known as TAS-102 or S95005) comprises the anti-neoplastic thymidine based nucleoside analogue, trifluridine (FTD) [Figure 1 (a)] and the thymidine phosphorylase inhibitor tipiracil hydrochloride (TPI) [Figure 1 (b)] at a molar ratio of 1:0.5 (weight ratio, 1:0.471).  **Chemical Structure of (a) FTD and (b) TPI.**

	Summary of mode of action Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a Deoxyribonucleic Acid (DNA) substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by Thymidine Phosphorylase (Tpase) and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the Tpase inhibitor, tipiracil hydrochloride. In nonclinical studies, trifluridine/tipiracil hydrochloride demonstrated antitumour activity against both 5-fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines. The cytotoxic activity of trifluridine/tipiracil hydrochloride against several human tumour xenografts correlated highly with the amount of trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.
Hyperlink to the Product Information	Module 1.3.1
Indication(s) in the EEA	Current Colorectal cancer Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents . Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. Gastric cancer Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see section 5.1).

Dosage in the EEA	Current The recommended starting dose of Lonsurf in adults**,** as monotherapy or in combination with bevacizumab, is 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity (see section 4.4). When Lonsurf is used in combination with bevacizumab for the treatment of CRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks. Please refer to the full product information for bevacizumab (see section 5.1). The dosage is calculated according to Body Surface Area (BSA) (see table 1 in the section 4.2 of the EU SmPC). The dosage must not exceed 80 mg/dose. Dosing adjustments may be required based on individual safety and tolerability. A maximum of 3 dose reductions are permitted to a minimum dose of 20 mg/m2 twice daily. Dose escalation is not permitted after it has been reduced. In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria.
Pharmaceutical form(s) and strengths	Current 15 mg/6.14 mg and 20 mg/8.19 mg film-coated tablets, for oral administration. Each 15 mg/6.14 mg film-coated tablet contains 15 mg trifluridine and 6.14 mg tipiracil (as hydrochloride). Each 20 mg/8.19 mg film-coated tablet contains 20 mg trifluridine and 8.19 mg tipiracil (as hydrochloride).
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SI – Epidemiology of the indications and target populations

Treatment of metastatic colorectal cancer in adults

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

Lonsurf proposed new indication is in combination with bevacizumab for the treatment of adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

The intended purpose of the medicinal product is to delay progression of disease and prolong Overall Survival (OS).

Incidence:

Colorectal cancer is the third most frequently diagnosed cancer and the second most common one in terms of mortality in the world. Globally more than 1.85 million new cases and 916 000 deaths were estimated to occur in 2020. In the European Union (EU), 332 170 new cases (11.3% of total cancer cases) were expected in 2020 (Sung, 2021).

Almost 50% of CRC patients will develop metastases and approximately 20-25% of patients have metastatic disease at the time of initial presentation. For patients with unresectable disseminated cancer, the disease is almost always incurable (Cervantes, 2022).

Prevalence:

The 5-year prevalence of CRC (i.e. number of patients surviving 5 or more years following a CRC diagnosis) in the EU was estimated to be 996 985 in total (557 410 men and 439 575 women) in 2020 (Sung, 2021).

Demographics of the population in the treatment of metastasic CRC in adults – age, gender, racial and/or ethnic origin and risks factors for the disease:

Colorectal cancer is more common in males than females. In Slovakia and Hungary the estimated incidence in men was higher than for men in other EU Member States. In Norway, Denmark and The Netherlands whilst incidence was lower in women than men, the incidence in women was higher than those of women in other Member States (Sung, 2021).

The risk of developing colorectal cancer increases with age. Ninety (90)% of patients diagnosed with CRC are over the age of 50 years (American cancer society, 2014). Since the 1990s, the rate of CRC cancer has been rising steadily among adults younger than 50, including in Europe. The cause for this trend needs to be elucidated and screening guidelines may need to be reconsidered (Vuik, 2019).

Incidence increase with industrialisation, urbanization and the Western lifestyle, such as unhealthy diet, obesity and tobacco consumption (Favoriti, 2016). It has been more common in

higher income countries but is now increasing in the middle and low income countries. It remains relatively uncommon in Africa and much of Asia (World Cancer Research Fund, 2011).

In the United States (US), African Americans have the highest incidence of CRC (World Cancer Research Fund, 2011).

Jews of Eastern Europe descent (Ashkenazi Jews) have one of the highest colorectal risks of any ethnic group in the world. Several gene mutations leading to an increased risk of CRC have been found in this group. The most common of these changes, the *11307K Adenomatous Polyposis Coli (APC)* mutation, is present in about 6% of American Jews (American cancer society, 2014).

A number of factors have been identified which increase the risk of developing CRC (World Cancer Research Fund, 2011):

- Personal or family history of adenomatous polyps or CRC caused by mutations in the *APC* gene (about 1% of all CRCs).
- History of ulcerative colitis or Crohn's disease.
- Hereditary Non-Polyposis Colorectal Cancer (HNPCC): HNPCC, also known as Lynch syndrome, accounts for about 2% to 4% of all CRCs. In most cases, this disorder is caused by an inherited defect in either the gene *mutL Homolog 1* (*MLH1)* or the gene *mutS Homolog 2* (*MSH2)*.
- Peutz-Jeghers syndrome: These patients are at greatly increased risk for CRC, as well as several other cancers, which appear in these patients at a younger age than in the general population. This syndrome is caused by mutations in the gene *Serin/Threonine Kinase 1 (STK1)*.
- *mutY Homolog (MUTYH)*-associated polyposis: This syndrome is caused by mutations in the gene *MUTYH*.
- Type 2 diabetes. Both type 2 diabetes and CRC share some of the same risk factors (such as excess weight). But even after taking these factors into account, people with type 2 diabetes still have an increased risk. They also tend to have a less favourable prognosis (outlook) after diagnosis.
- Lifestyle factors such as high-fat diet, low fiber, obesity, inactivity, smoking and alcoholic drinks are major contributors to the incidence of CRC.

<u>The main existing treatment options:</u>

The treatment of metastatic CRC is dependent upon many factors including the disease stage at presentation and the extent of the metastatic spread.

As stated above, almost 50% of CRC patients will develop metastases and approximately 20-25% of patients have metastatic disease at the time of initial presentation.

For a small proportion of patients with resectable metastasis, surgery is the treatment option of choice. This may consist of local resection if a small number of metastases are present, radiofrequency ablation, ethanol ablation, cryosurgery or hepatic artery embolisation.

In patients with unresectable disease, chemotherapy is the mainstay of treatment. Various combinations of the drugs below may be used for the treatment of these patients at some point during the duration of their disease (Cervantes, 2022). The choice of chemotherapy is based upon

the consideration of the goals of therapy, the type and timing of prior therapies, and the differing toxicity profiles of the constituent drugs. Historically, a combined regimen containing a fluoropyrimidine such as Fluorouracil (5-FU) formed the backbone of chemotherapy for decades:

FOLFOX: Folinic Acid (FOL), Fluorouracil (5-FU) and Oxaliplatin (OX)

FOLFIRI: Folinic Acid (FOL), Fluorouracil (5-FU) and Irinotecan (IRI)

FOLFOXIRI: Folinic Acid (FOL), Fluorouracil (5-FU), Oxaliplatin (OX) and Irinotecan (IRI)

However, the introduction of monoclonal antibodies targeting VEGF receptor (bevacizumab, ramucirumab), have served to improve outcomes in these patients.

Mutations of the KRAS gene (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) are present in ~60% of colorectal cancers, and are an important predictor of non-response to treatment to EGFR inhibitors. The use of EGFR inhibitors (cetuximab, panitumumab) have shown improved clinical outcomes when combined with cytotoxic therapies for a subset of mCRC patients with wild-type KRAS tumours (Baldus, 2010).

Following progression after two lines of treatment with standard chemotherapies, an increasing number of patients with mCRC can receive 3 or more lines of therapy (Bekaii-Saab, 2019). Treatments in this setting include regorafenib (a multitargeted tyrosine kinase inhibitor), trifluridine/tipiracil (FTD/TPI) monotherapy, and for specific subgroups of patients, antibodies that target EGFR for patients with RAS wild-type tumours (if no prior exposure), and anti-programmed cell death protein 1 inhibitors for patients with microsatellite instability-high mCRC (Cervantes, 2022).

Clinical trials of emerging agents, new treatment combinations, and novel therapies are still needed to continue the efforts to improve outcomes for patients with mCRC (Cervantes, 2022).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Colorectal cancer was responsible for more than 153 000 deaths in the EU in 2020. This represents 12% of all cancer deaths (Sung, 2021).

Five-year survival rates by the Tumour, Nodes, Metastases (TNM) Classification of Malignant Tumours stage are approximately 74% for Stage 1 disease, 32-67% for Stage II disease, 28-74% for Stage III disease but only 6% for Stage IV disease (Edge, 2010).

Important co-morbidities:

Comorbidities in the target population include those common in the over 50 age group such as cardiovascular disease including hypertension, cardiac arrhythmias, cardiac failure, diabetes, musculoskeletal disorders, impaired renal function, depression/anxiety and dementia.

Treatment of metastatic gastric cancer (including gastro-esophageal-junction adenocarcinomas) in adults

Lonsurf is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents).

Incidence:

Gastric cancer (also known as stomach cancer) is the fifth most common cancer and the third most common cause of cancer death worldwide (Ferlay, 2013).

The incidence shows wide geographical variation. The high-risk areas include Eastern Asia, Eastern Europe and South America. Globally more than 950 000 new cases were diagnosed in 2012 (Smyth, 2016). Of these, 82,000 cases occurred in European Union (EU) (Ferlay, 2013a).

A decline in Gastric Cancer (GC) incidence rate has been observed worldwide in the last decades. The general decrease has been explained by higher standards of hygiene, and by *Helicobacter pylori (H. pylori)* eradication. However, the incidence of gastric cardia cancers (including gastro-esophageal-junction (GEJ) adenocarcinomas) is on the rise (Sitarz, 2018).

Prevalence:

The 5 year prevalence of GC (i.e. number of patients surviving 5 or more years following a GC diagnosis) in the EU is estimated to be 119,000 in total (74,000 men and 45,000 women) (Ferlay, 2013a).

Demographics of the population in the treatment of metastasic GC in adults – age, gender, racial and/or ethnic origin and risk factors for the disease:

GC mostly affects older people. Most people diagnosed with GC are in their 60s and 80s. Men are twice as likely to develop GC as women (Brenner, 2009). GC is more common in black, Hispanic, and Asian people than in white people (Karimi, 2014).

A number of factors have been identified which increase the risk of developing GC. *H. pylori* infection is the major risk factor associated with non-cardia GC. Smoking has also been implicated as a risk factor for non-cardia cancer. Furthermore, host genetic polymorphisms have an impact on host responses to gastric inflammation and acid secretion, thereby interacting with *H. pylori* infection and other environmental factors in gastric carcinogenesis.

In contrast to non-cardia cancer, *H. pylori* infection does not play an important role in cardia cancer, with obesity and smoking identified as the main risk factors. Although dietary, lifestyle and metabolic risk factors have been identified, and addressing these lifestyle and metabolic risk factors may contribute to health, the actual impact in terms of cancer prevention is unclear (Ang, 2014).

GC demonstrates familial aggregation in around 10% of cases, and an inherited genetic predisposition is found in a small proportion of cases (1-3%); relevant syndromes include hereditary non-polyposis colorectal cancer, Familial adenomatous polyposis (FAP) colorectal cancer, hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) and Peutz Jegher's syndrome (Smyth, 2016).

The main existing treatment options:

Currently, patients with GC can be cured only when diagnosed with early stage disease in which a complete resection of the tumor can be achieved. The majority of patients will ultimately relapse following resection (Smyth, 2016). Furthermore, approximately half of patients will have advanced disease, not eligible for resection, at diagnosis (Ajani, 2016). Patients with inoperable locally advanced and/or metastatic (stage IV) disease should be considered for chemotherapy, which has shown improved survival and quality of life compared with Best Supportive Care (BSC) alone (Smyth, 2016).

Standard chemotherapy regimens for advanced and/or metastatic GC include doublet and triplet combinations with fluoropyrimidines, platinum derivatives, and taxanes, or irinotecan.

Based on the results of the ToGA study (Bang, 2010), the addition of trastuzumab, is a humanized recombinant monoclonal antibody that targets the HER2 protein, to chemotherapy has become standard of care, where available, for first-line treatment of patients with HER2-neu-positive (HER2+) advanced and/or metastatic GC.

For patients who progress following first-line chemotherapy, second-line treatment has been shown to further prolong survival and improve quality of life for many patients. Selection of treatment is depending on prior therapy and Performance Status (PS) at baseline, but may include the anti-VEGF monoclonal antibody ramucirumab and/or paclitaxel, irinotecan, or docetaxel (Smyth, 2016) Ramucirumab, has been shown to increase OS when administered alone (Fuchs, 2014) or in combination with paclitaxel (Wilke, 2014) in patients who have progressed following first-line therapy; and was recently approved for second-line therapy of gastric cancer for patients who are of PS 0–1.

However, after failure of first- and second-line therapies, there are neither approved nor standard 3rd line treatments.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The majority of Stage IB and II disease and certain Stage III GC are resectable. However, even in patients who have undergone potentially curative surgery, 5-year survival is low. Additionally, many patients present with metastatic disease at first diagnosis, with a 5-year survival rate of less between 10% and 30% (Sitarz R, 2018).

GC cancer was responsible for 723,000 deaths in both sexes worldwide in 2012. This represents 8.8% of all cancer deaths. The estimated mortality rate was 58,000 in both sexes in EU in 2012 (Ferlay, 2013a).

Important co-morbidities:

Comorbidities in the target population include those common in the over 50 age group such as cardiovascular diseases including hypertension, cardiac arrhythmias, cardiac failure, diabetes, musculoskeletal disorders, impaired renal function, depression/anxiety and dementia.

Part II: Module SII – Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- key issues identified from acute or repeat-dose toxicity studies

Single-dose toxicity

The toxicities of trifluridine-tipiracil and FTD alone were found to be very similar, with no exacerbation of effects when FTD was administered in conjunction with TPI.

The approximate lethal dose of trifluridine-tipiracil after single administration was 2000 mg/kg (FTD equivalent) in rats and dogs. The main target organ seemed to be digestive tract in both species.

Gastrointestinal (GI) effects

In non-clinical repeat-dose studies, diarrhoea, vomiting, decreased food consumption and decreased body weight were observed.

Histology revealed reversible necrosis of glandular epithelial cells and an increase in apoptotic bodies throughout the GI tract.

Inflammation in the GI tract was observed following repeated administration of TPI alone in monkeys at doses of ≥ 300 mg/kg/day, but this dose is greater than the level of TPI contained in the maximum dose of trifluridine-tipiracil in all repeated dose studies, which explains the absence of an exacerbation of GI tract findings in studies using trifluridine-tipiracil compared to FTD alone.

Regarding the human usage, disorders of the GI system are common to compounds which target cell proliferation, and similar to side effects of many other existing cytotoxic anticancer drugs.

Gastrointestinal effects (nausea, vomiting and diarrhoea) are considered as Important Identified Risk for trifluridine-tipiracil, but are managed through routine pharmacovigilance activities and rourine risk minimization measures, and therefore not characterized in this updated version of the RMP.

Lymphatic and haematopoietic systems

Following repeated administrations, the lymphatic and haematopoietic systems in addition to the GI tract were identified as target tissues/organs in rats, dogs and monkeys with both trifluridine-tipiracil and FTD alone.

In the lymphatic and haematopoietic tissues, reversible dose dependent decreases in the White blood cells (WBC) count, red blood cell count, reticulocyte percentage, haemoglobin level and haematocrit were observed, and atrophy of the thymus, spleen and lymph nodes and decrease in haematopoietic cells of the bone marrow were observed histopathologically.

In human usage, disorders in the lymphatic and haematopoietic tissues are common to compounds which target cell proliferation, and similar to side effects of many other existing cytotoxic anticancer drugs.

Bone marrow suppression and Infection are considered as Important Identified Risks for trifluridine-tipiracil but both are managed through routine pharmacovigilance activities and routine minimization measures, and therefore not characterized in the RMP.

- reproductive/developmental toxicity

In non-clinical studies, no effect on fertility was observed with trifluridine-tipiracil.

However, foetal weight loss and delayed ossification were observed as well as a significant increase in post-implantation loss and marked increases in the incidences of foetuses with external abnormalities, visceral abnormalities, and skeletal abnormalities. Trifluridine-tipiracil has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure.

Distribution data in animals have shown excretion of trifluridine-tipiracil and/or its metabolites in breast milk.

Developmental toxicity/Use in pregnant women is considered as Important Potential Risk for this RMP. Use in breast feeding women is managed through routine pharmacovigilance activities and routine minimization measures, and therefore not characterized in the RMP.

- genotoxicity

From non-clinical studies trifluridine-tipiracil is mutagenic and clastogenic. Both trifluridine-tipiracil and FTD alone had reversed mutation-inducing potential and chromosomal aberration-inducing potential (*in vitro* and *in vivo*).

TPI was non-genotoxic.

Trifluridine-tipiracil is indicated for the treatment of adult patients with metastatic CRC or metastatic GC who are refractory to or unable to tolerate standard therapies. The genotoxic potential of trifluridine-tipiracil in these patient populations is not considered to be an important safety concern.

- carcinogenicity

According to the ICH S9 guideline, no carcinogenicity studies were conducted due to the genotoxicity of FTD.

Safety pharmacology

- cardiovascular system, including potential effect on the QT interval

In accordance with International Conference on Harmonisation (ICH) S9, there is no requirement to conduct stand-alone safety pharmacology studies for therapeutics intended to treat patients with advanced cancer. However, prior to ratification of ICH S9 in 2010, trifluridine-tipiracil was assessed in stand-alone safety pharmacology studies including a modified Irwin test, measurement of body temperature and respiratory parameters in the rat, as well as cardiovascular (electrocardiography (ECG)) and blood pressure measurements in telemetered, conscious

monkeys and an *in vitro* human Ether-a-go-go-Related Gene (hERG) potassium channel assay were conducted.

The effect of FTD was assessed *in vitro* on the peak hERG tail current recorded from a HEK293 cell line stably expressing the hERG potassium channel. FTD was tested at concentrations of 3, 30 and 300 µmol/L and the effect compared to vehicle treated cells. There was no significant difference in hERG inhibition between FTD and vehicle treated cells. FTD inhibited hERG currents by 1.8%, 1.8% and 2.5% at concentrations of 3, 30 and 300 µmol/L, respectively (corrected for vehicle inhibition of 1.5%). Under the condition of the study, FTD is considered to have no effect on hERG current at concentrations up to 300µmol/L. Likewise; the effect of TPI was assessed *in vitro* at concentrations of 1, 10 and 100 µmol/L. There was no significant difference in hERG inhibition between TPI and vehicle treated cells. TPI inhibited hERG currents by -0.8%, 1.8% and 0.4% at concentrations of 1, 10 and 100 µmol/L, respectively (corrected for vehicle inhibition of 2.1%). Under the condition of the study, TPI is considered to have no effect on hERG current at concentrations up to 100 µmol/L.

The effects of oral, gavage administration of FTD on blood pressure, heart rate and ECG parameters (including QT, QTc, PR and QRS interval) were evaluated in 4 male, naïve cynomolgus monkeys implanted with a telemetry device, at dose levels of 0 (vehicle control), 6.8, 27.2 and 108.8 mg/kg. There were no treatment-related differences between the vehicle group and any of the FTD treated animals, in any of the cardiovascular parameters examined, at any timepoint. Under the conditions of the study, oral administration of FTD at dose levels of up to 108.8 mg/kg produced no effects on cardiovascular parameters in the conscious monkey. Similarly, the effects of TPI were evaluated in 4 males, naïve cynomolgus monkeys at dose levels of 0 (vehicle control), 62.5, 250 and 1000 mg/kg. There were no discernible differences between the vehicle group and any of the TPI treated animals, in any of the cardiovascular parameters examined, at any timepoint. Under the conditions of the study, oral administration of TPI at dose levels of up to 1000 mg/kg produced no effects on cardiovascular parameters in the conscious monkey. The observations reported from these safety pharmacology assessments in both rat and non-human primate, together with investigation of hERG current *in vitro*, were largely unremarkable and did not indicate any specific concerns with respect to human safety.

In vitro and non-clinical studies did not reveal any evidence of cardiovascular toxicity. A Phase I clinical study (TAS-102-103) was performed to evaluate the cardiac safety of orally administered trifluridine-tipiracil in patients with advanced solid tumours. The results of this study demonstrated that:

- Trifluridine-tipiracil following a single dose or following multiple doses had no clinically relevant QtcI, QTcF, or QTcB prolongation effect compared to placebo.
- There was no clinically relevant relationship between plasma concentrations of trifluridine-tipiracil and effect on QTc interval as evidenced by the upper bounds of the 1-sided 95% Confidence Intervals (Cis) for the differences in time-matched baseline-subtracted 12-lead Holter QtcI, QTcF, and QTcB intervals between trifluridine-tipiracil and placebo that did not exceed 20 millisecond (msec) at any time point.
- Trifluridine-tipiracil does not appear to be arrhythmogenic as evidenced by the absence of Adverse Events (Aes) of ventricular tachycardia, ventricular fibrillation, syncope, and seizure.

Current data indicates that cardiovascular toxicity is not a safety concern.

Mechanisms for drug interactions:

There was no evidence that FTD and TPI are metabolized by Cytochrome (CYP) enzymes (Study No. 12DB03 and 99C42). Similarly, neither FTD nor TPI was a substrate for, or inhibitor of, human uptake and efflux transporters studied in vitro, except for organic cation transporter 2 (OCT2), and thus neither would be expected to be subject to a transporter-mediated drug interaction. No effect on the Pharmacokinetics (PK) of other drugs would be expected because the inhibitory constant of TPI against OCT2 was much higher than TPI Cmax observed in clinical studies (TAS-102-102).

In a drug interaction study, when FTD was administered concomitantly with deoxythymidine (dThd) analogue-type antiviral drugs in vitro, azidothymidine (AZT, zidovudine) attenuated the inhibitory action of FTD at 3μM or more (close to established clinical concentrations) on human colon cancer (HCT116) and human gastric cancer (NUGC-3) cell proliferation, suggesting that the anti-tumour effects of TAS-102 could be attenuated when AZT is used concomitantly in clinical practice. However, treatment with TAS-102 in combination with AZT in rats did not influence the toxicity relative to TAS-102 alone (Study No.13CC20).

Due to the competitive inhibition of thymidine kinase by Lonsurf, there is a risk that the activity of thymidine analogues or of Lonsurf will be reduced when taken simultaneously. However, this is not considered to be an important safety concern.

Part II: Module SIII – Clinical trial exposure

- **Legacy studies**

Five (5) legacy Phase 1 clinical trials conducted in patients with solid tumors and one legacy Phase II clinical trial conducted in patients with gastric cancer were completed between 1999 and 2008 in the United States. The Table below sets out a summary of clinical exposure to trifluridine-tipiracil in the legacy studies.

Exposure by indication, dose regimen and prior therapies of legacy studies with trifluridine-tipiracil

Trial	Dose Regimen/Dosage	N	Malignancy (% of patients)	Prior therapies (median)
Phase I				
TAS-102-9801	2 weeks with 1 week rest, repeated every 3 weeks / qd (every day)	14	Colorectal (100%)	4
TAS-102-9802	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / qd	24	Colorectal (83.3%)	3.5
TAS-102-9803	5 days every 3 weeks /qd	39	Colorectal (82.1%)	4
TAS-102-9804	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / bid (twice daily)	19	Breast (100%)	5
TAS-102-9805	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / tid (three times a day)	15	Colorectal (60%)	3
Phase II				
TAS-102-9806	50 mg/m^2 daily administered orally in 2 daily doses from Days 1 through 5, with Days 6 and 7 as rest days, for 2 weeks followed by a 2-week recovery period.	18	Metastatic gastric cancer	1

- **Completed clinical programme with a recommended starting dose at 35 mg/m^2/dose monotherapy or in combination with bevacizumab**

The following tables set out the clinical exposure for the current clinical development programme and represent patients receiving 35 mg/m^2/dose monotherapy in mCRC and mGC.

The safety data will be presented according to the five following groups:

mCRC Group 1: integrated trifluridine-tipiracil studies in patients with mCRC receiving starting dose of 35 mg/m^2/dose in monotherapy (TAS-102-J001-10040010, TAS-102-J003-10040030, TAS-102-J004-10040040, TPU-TAS-102-101, TPU-TAS-102-102, TPU-TAS-102-103, TPU-TAS-102-104, and TPU-TAS-102-301/RECOURSE). It should be noted that, whilst these studies were not limited to CRC patients, only the data from the CRC patients have been included in this group.

mCRC Group 2: integrated trifluridine-tipiracil from the 2 randomised, placebo controlled mCRC studies (TAS-102-J003-10040030 and TPU-TAS-102-301/RECOURSE).

mCRC RECOURSE: data from TPU-TAS-102-301 (RECOURSE) alone.

mCRC SUNLIGHT: data from CL3-95005-007 (SUNLIGHT) alone with trifluridine-tipiracil 35 mg/m^2/dose as recommended started dose either in monotherapy or in combination with bevacizumab.

mGC TAGS: data from from the randomised, placebo controlled mGC study (TO-TAS-102-302/TAGS) alone.

Clinical trial exposure for mCRC

List of completed studies in mCRC with 35 mg/m2/dose of trifluridine-tipiracil (monotherapy or in combination) or placebo

Study Protocol	Number of mCRC Patients included and receiving 35 mg/m^2/dose of trifluridine-tipiracil or placebo)	Study design and type of control	Included patients
TAS-102-J001-10040010	5	Phase 1, open-label, non-randomised, dose-finding.	Patients with confirmed solid tumours responding poorly to standard treatment.
TAS-102-J003-10040030	170 (FTD/TPI, 113; placebo, 57)	Phase 2, placebo-controlled, multicentre, double-blind, randomized.	Patients with unresectable advanced/ recurrent CRC who had received ≥2 chemotherapy regimens and who were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin.
TAS-102-J004-10040040	5	Phase 1, open-label, randomised, crossover (PK period) with open-label extension.	Patients with solid tumours (excluding gastric cancer and status post gastrectomy).

Study Protocol	Number of mCRC Patients included and receiving 35 mg/m²/dose of trifluridine-tipiracil or placebo)	Study design and type of control	Included patients
TPU-TAS-102-101	24	Phase 1, open-label, non-randomised, dose-escalation.	Patients with refractory metastatic CRC (mCRC) who had received ≥2 prior lines of chemotherapy for mCRC including fluoropyrimidine, oxaliplatin, and irinotecan.
TPU-TAS-102-102	29	Phase 1, open-label, randomised, parallel group (PK contribution part) followed by open-label extension part.	Patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists.
TPU-TAS-102-103	33	Phase 1, open-label with single-blind placebo run-in (Cycle 1) with open-label extension.	Patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists.
TPU-TAS-102-104	19	Phase 1, open-label, randomised, 2-sequence, 3-period crossover with open-label extension.	Patients with advanced solid tumours (excluding breast cancer) for which no standard therapy exists.
TPU-TAS-102-301 [RECOURSE]	798 (FTD/TPI, 533*; placebo, 265) **534 were randomized and 533 received at least one dose of FTD/TPI*	Phase 3, placebo-controlled, multicentre, double-blind, parallel, randomized. PK assessments at selected sites.	Patients with mCRC who had received ≥2 prior regimens of standard chemotherapies (including fluoropyrimidine, irinotecan, and oxaliplatin, an anti-VEGF monoclonal anti-body; and at least 1 anti-EGFR monoclonal anti-bodies for KRAS wild-type patients) and were refractory to or failing those chemotherapies.
CL3-95005-007 [SUNLIGHT]	492 (FTD/TPI, 246; FTD/TPI+Bevacizumab ,246)	Phase 3, multicentre, open-label, parallel, randomized.	Patients with mCRC who had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer (including fluoropyrimidine, irinotecan, and oxaliplatin, and an anti-VEGF monoclonal anti-body and/or an anti-EGFR monoclonal anti-body for RAS wild-type patients)

Exposure to study treatment for mCRC: cycles, weeks of exposure and cumulative dose

	Group 1 (Integrated FTD/TPI -PK studies[b])		**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301)**		**RECOURSE (TPU-TAS-102-301)**		**SUNLIGHT** (CL3-95005-007)	
	FTD/TPI N=761	**FTD/TPI %**	**FTD/TPI N=646**	**FTD/TPI %**	**FTD/TPI N=533**	**FTD/TPI %**	**FTD/TPI N=492**	**FTD/TPI %**
Cycle initiated[a]	24[b]	3.2[b]						
1	753	98.9	646	100	533	100	492	100
2	637	83.7	545	84.4	466	87.4	452	91.9
3	330	43.4	288	44.6	231	43.3	291	59.1
4	269	35.3	236	36.5	192	36.0	253	51.4
>4	172	22.6	152	23.5	117	22.0	183	37.2
Maximum # cycle initiated	8 [c]	1.1 [c]						
1	116	15.2	101	15.6	67	12.6	39	7.9
2	307	40.3	257	39.8	235	44.1	163	33.1
3	61	8.0	52	8.0	39	7.3	37	7.5
4	97	12.7	84	13.0	75	14.1	70	14.2
5	40	5.3	31	4.8	20	3.8	26	5.3
6	44	5.8	41	6.3	37	6.9	46	9.3
7	23	3.0	22	3.4	16	3.0	14	2.8
8	22	2.9	18	2.8	12	2.3	28	5.7
9	9	1.2	9	1.4	7	1.3	9	1.8
10	14	1.8	13	2.0	10	1.9	15	3.1
11	11	1.4	11	1.7	10	1.9	6	1.2

	Group 1 (Integrated FTD/TPI -PK studies[b])		**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301)**		**RECOURSE (TPU-TAS-102-301)**		**SUNLIGHT** (CL3-95005-007)	
12	3	0.4	3	0.5	2	0.4	13	2.6
13	3	0.4	2	0.3	1	0.2	6	1.2
14	1	0.1	0	0	0		10	2.0
15	0	0	0	0	0		4	0.8
16	1	0.1	1	0.2	1	0.2	2	0.4
17	0	0	0	0	0		4	0.8
18	1	0.1	1	0.2	1	0.2	0	0
Cycles per patient								
Total cycles initiated	2591		2234		1828		2315	
Mean (Standard Deviation (SD))	3.4 (2.57)		3.5 (2.61)		3.4 (2.56)		4.71 (3.61)	
Median	2.0		2		2.0		4.0	
Min, Max	1,18		1,18		1,18		1,17	
Weeks[d, e]								
Total weeks	9540.3		8331.3		6743.6		10212.0	
Mean (SD)	12.54 (12.079)		12.90 (12.367)		12.65 (11.965)		20.76 (16.38383)	
Median	6.71		6.71		6.71		16.14	
Min, Max	0.1,78.0		0.1, 78.0		0.1, 78.0		0.4, 80.3	
Total dose administered (mg/m^2)								
Mean (SD)	2202.5 (1684.32)		2258.4 (1708.57)		2251.2 (1674.53)		3075.2 (2385.56)	
Median	1401.5		1407.1		1405.8		2378.4	

	Group 1 (Integrated FTD/TPI -PK studies[b])	**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301)**	**RECOURSE (TPU-TAS-102-301)**	**SUNLIGHT** (CL3-95005-007)
Min, Max	66,12470	68,12470	133,12470	17,11769

[a] Patients counted in each cycle initiated (at least one dose of FTD/TPI administered)
[b] 24 patients in Group 1 were enrolled in studies with a crossover pharmacokinetic (PK) phase prior to initiation of the first cycle of treatment: Study TPU-TAS-102-104 (n=19) and Study J004-10040040 (n=5).
[c] 3 of the 19 Group 1 patients from Study TPU-TAS-102-104 discontinued after the PK Phase; and only PK phase data are included in the integrated database for the 5 Group 1 patients from Study J004-10040040. Therefore, for these 8 patients, the PK phase represents their maximum exposure to FTD/TPI in the integrated ISS database.
[d] (Date of last dose of study treatment-date of first dose of study treatment +1)/7
[e] For Sunlight: (([min(first intake date of the last cycle + 27 days, death date)-first trifluridine/tipiracil intake date]+1)/7)

Exposure by gender for mCRC

	Group 1 (Integrated FTD/TPI studies) FTD/TPI		**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301) FTD/TPI**		**RECOURSE (TPU-TAS-102-301) FTD/TPI**		**SUNLIGHT** (CL3-95005-007) FTD/TPI	
	M	F	M	F	M	F	M	F
Cycles per Patient:								
Total Cycles Initiated	1552	1039	1345	889	1108	720	1204	1111
Mean (SD)	3.4 (2.48)	3.4 (2.70)	3.4 (2.51)	3.5 (2.77)	3.4 (2.46)	3.5 (2.72)	4.7 (3.61)	4.7 (3.62)
Median	2.0	2.0	2.0	2.0	2.0	2.0	4.0	4.0
Min, Max	1, 14	1, 18	1, 13	1, 18	1, 13	1, 18	1, 17	1, 17
Total weeks[a, b]	5678.0	3862.3	4983.3	3348.0	4058.4	2685.1	5311.1	4900.9
Mean (SD)	12.48 (11.536)	12.62 (12.863)	12.78 (11.741)	13.08 (13.285)	12.45 (11.300)	12.97 (12.965)	20.75 (16.16)	20.77 (16.64)
Median	6.71	6.71	6.71	6.71	6.71	6.71	16.4	16.0
Min, Max	0.1, 62.1	0.1, 78.0	0.1, 62.1	0.1, 78.0	0.1, 59.7	0.1, 78.0	0.4, 80.3	2.4, 75.0

[a] (Date of last dose of study treatment – date of first dose of study treatment + 1) / 7
[b] For Sunlight: (([min(first intake date of the last cycle + 27 days, death date)-first trifluridine/tipiracil intake date]+1)/7)

Exposure by age for mCRC

	Group 1 (Integrated FTD/TPI studies) FTD/TPI	**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301) FTD/TPI**	**RECOURSE (TPU-TAS-102-301) FTD/TPI**	**SUNLIGHT** (CL3-95005-007) FTD/TPI
< 65 years				
N	436	360	299	275
Cycles per Patient:				
Total Cycles Initiated	1395	1172	971	1271
Mean (SD)	3.2 (2.39)	3.3 (2.40)	3.2 (2.41)	4.62 (3.57)
Median	2.0	2.0	2.0	4.0
Min, Max	1, 16	1, 16	1, 16	1, 17
Total weeks[a, b]	5003.3	4260.1	3503.3	5558.3
Mean (SD)	11.48 (11.197)	11.83 (11.353)	11.72 (11.272)	20.21 (15.97)
Median	6.36	6.57	6.29	16.0
Min, Max	0.1, 78.0	0.1, 78.0	0.1, 78.0	2.4, 74.9
≥ 65 years				
N	325	286	234	217
Cycles per Patient:				
Total Cycles Initiated	1196	1062	857	1044
Mean (SD)	3.7 (2.77)	3.7 (2.84)	3.7 (2.73)	4.81 (3.68)

	Group 1 (Integrated FTD/TPI studies) FTD/TPI	**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301) FTD/TPI**	**RECOURSE (TPU-TAS-102-301) FTD/TPI**	**SUNLIGHT** (CL3-95005-007) FTD/TPI
Median	2.0	2.0	2.0	4.0
Min, Max	1, 18	1, 18	1, 18	1, 17
Total weeks[a, b]	4537.0	4071.1	3240.3	4653.7
Mean (SD)	13.96 (13.054)	14.23 (13.437)	13.85 (12.721)	21.45 (16.89)
Median	7.71	7.64	7.0	17.0
Min, Max	0.1, 76.0	0.1, 76.0	0.6, 76.0	0.4, 80.3
65- < 75 years				
N	271	241	198	159
Cycles per Patient:				
Total Cycles Initiated	994	886	718	791
Mean (SD)	3.7 (2.74)	3.7 (2.78)	3.6 (2.71)	5.0 (3.80)
Median	2.0	2.0	2.0	4.0
Min, Max	1, 18	1, 18	1, 18	1, 17
Total weeks[a, b]	3771.7	3393.1	2712.0	3525.6
Mean (SD)	13.92 (12.818)	14.08 (13.092)	13.70 (12.570)	22.17 (17.51)
Median	7.57	7.57	6.93	17.14
Min, Max	0.6, 76.0	0.6, 76.0	0.6, 76.0	0.4, 80.3
≥ 75 years				

	Group 1 (Integrated FTD/TPI studies) FTD/TPI	**Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301) FTD/TPI**	**RECOURSE (TPU-TAS-102-301) FTD/TPI**	**SUNLIGHT** (CL3-95005-007) FTD/TPI
N	54	45	36	58
Cycles per Patient:				
Total Cycles Initiated	202	176	139	253
Mean (SD)	3.7 (2.95)	3.9 (3.15)	3.9 (2.89)	4.36 (3.31)
Median	3.0	3.0	3.0	3.5
Min, Max	1, 13	1, 13	1, 11	1, 14
Total weeks[a, b]	765.3	678.0	528.3	1128.1
Mean (SD)	14.17 (14.302)	15.07 (15.291)	14.67 (13.676)	19.45 (15.00)
Median	8.79	9.57	9.71	15.93
Min, Max	0.1, 62.1	0.1, 62.1	1.7, 52.6	4.0, 63.0

[a] *(Date of last dose of study treatment – date of first dose of study treatment + 1) / 7.*
[b] *For Sunlight: (([min(first intake date of the last cycle + 27 days, death date)-first trifluridine/tipiracil intake date]+1)/7)*

Exposure by ethnic origin for mCRC Group 1 (Integrated trifluridine-tipiracil studies)

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian/Oriental FTD/TPI**	**Not collected FTD/TPI**
N	401	12	308	40
Cycles per Patient:				

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian/Oriental FTD/TPI**	**Not collected FTD/TPI**
Total Cycles Initiated	1331	35	1072	153
Mean (SD)	3.3 (2.41)	2.9 (1.73)	3.5 (2.82)	3.8 (2.30)
Median	2.0	2.0	2.0	3.0
Min, Max	1, 14	1, 6	1, 18	1, 11
Total weeks[a]	4747.4	116.0	4105.6	571.3
Mean (SD)	11.84 (10.895)	9.67 (7.219)	13.33 (13.757)	14.28 (10.285)
Median	6.57	6.57	6.71	12.00
Min, Max	*0.1, 59.3*	*1.7, 23.7*	*0.1, 78.0*	*1.7, 45.1*

[a] *(Date of last dose of study treatment – date of first dose of study treatment + 1) / 7.*

Exposure by ethnic origin mCRC Group 2 (TAS102-J003-10040030 and TPU-TAS-102-301)

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian/Oriental FTD/TPI**	**Not collected FTD/TPI**
N	305	4	297	40
Cycles per Patient:				
Total Cycles Initiated	1015	15	1051	153
Mean (SD)	3.3 (2.41)	3.8 (2.63)	3.5 (2.85)	3.8 (2.30)
Median	2.0	4.0	2.0	3.0
Min, Max	1, 13	1, 6	1, 18	1, 11
Total weeks[a]	3668.6	52.1	4039.3	571.3

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian/Oriental FTD/TPI**	**Not collected FTD/TPI**
Mean (SD)	12.03 (10.990)	13.04 (11.215)	13.60 (13.874)	14.28 (10.285)
Median	6.57	13.36	6.71	12.00
Min, Max	0.1, 51.0	1.7, 23.7	0.1, 78.0	1.7, 45.1

[a] *(Date of last dose of study treatment – date of first dose of study treatment + 1) / 7.*

Exposure by ethnic origin for mCRC RECOURSE (TPU-TAS-102-301)

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian/Oriental FTD/TPI**	**Not collected FTD/TPI**
N	305	4	184	40
Cycles per Patient:				
Total Cycles Initiated	1015	15	645	153
Mean (SD)	3.3 (2.41)	3.8 (2.63)	3.5 (2.85)	3.8 (2.30)
Median	2.0	4.0	2.0	3.0
Min, Max	1, 13	1, 6	1, 18	1, 11
Total weeks[a]	3668.6	52.1	2451.6	571.3
Mean (SD)	12.03 (10.990)	13.04 (11.215)	13.32 (13.757)	14.28 (10.285)
Median	6.57	13.36	6.71	12.00
Min, Max	0.1, 51.0	1.7, 23.7	1.1, 78.0	1.7, 45.1

[a] *(Date of last dose of study treatment – date of first dose of study treatment + 1) / 7.*

Exposure by ethnic origin for mCRC SUNLIGHT (CL3-95005-007)

	Caucasian/White FTD/TPI	**Black/African American FTD/TPI**	**Asian FTD/TPI**	**American Indian or Alaska FTD/TPI**	**Other FTD/TPI**	**Not collected**
N	435	7	1	1	13	35
Cycles per Patient:						
Total Cycles Initiated	2094	25	*	*	66	122
Mean (SD)	4.81 (3.63)	3.57 (2.23)	*	*	5.08 (4.29)	3.49 (3.27)
Median	4.0	3.0	*	*	3.0	2.0
Min, Max	1, 17	1, 8	*	*	1, 17	1, 16
Total weeks[a]	9255.9	103.6	*	*	290.6	527.1
Mean (SD)	21.28 (16.50)	14.80 (9.75)	*	*	22.35 (19.39)	15.06 (14.20)
Median	17.00	12.00	*	*	14.86	9.00
Min, Max	0.4, 80.3	3.6, 34.0	*	*	4.0, 74.9	2.4, 66.0

[a] *(([min(first intake date of the last cycle + 27 days, death date)-first trifluridine/tipiracil intake date]+1)/7)*
**Protected Personal Data (PPD)*

Exposure by Renal Impairment (baseline creatinine clearance (CLcr) for mCRC

	Group 2 (TAS102-J003-10040030, and TPU-TAS-102-301) FTD/TPI			**RECOURSE (TPU-TAS-102-301) FTD/TPI**			**SUNLIGHT (CL3-95005-007) FTD/TPI**		
Creatinine clearance (ml/min)	**≥ 90**	**60-89**	**30-59**	**≥ 90**	**60-89**	**30-59**	**≥ 90**	**60-89**	**30-59**

	Group 2 (TAS102-J003-10040030, and TPU-TAS-102-301) FTD/TPI			**RECOURSE (TPU-TAS-102-301) FTD/TPI**			**SUNLIGHT (CL3-95005-007) FTD/TPI**		
N	356	221	67	306	178	47	265	168	58
Cycles per Patient:									
Total Cycles Initiated	1196	777	258	1011	613	201	1184	875	254
Mean (SD)	3.4 (2.36)	3.5 (2.74)	3.9 (3.39)	3.3 (2.31)	3.4 (2.63)	4.3 (3.56)	4.47 (3.30)	5.21 (4.17)	4.38 (3.13)
Median	2.0	2.0	2.0	2.0	2.0	3.0	3.0	4.0	4.0
Min, Max	1, 13	1, 16	1, 18	1, 13	1, 16	1, 18	1, 17	1, 17	1, 14
Total weeks[a, b]	4351.3	2985.6	987.0	3640.3	2314.7	781.1	5205.9	3867.6	1129.6
Mean (SD)	12.22 (10.855)	13.51 (13.343)	14.73 (16.051)	11.90 (10.571)	13.00 (12.612)	16.62 (16.694)	19.64 (14.94)	23.02 (18.92)	19.48 (14.21)
Median	6.64	6.71	7.00	6.36	6.71	10.29	15.14	17.00	17.64
Min, Max	0.1, 61.0	0.3, 78.0	0.1, 76.0	0.1, 61.0	0.3, 78.0	0.7, 76.0	2.4, 74.9	0.4, 80.3	4.0, 63.0

[a] *(Date of last dose of study treatment – date of first dose of study treatment + 1) / 7.*
[b] *For Sunlight: (([min(first intake date of the last cycle + 27 days, death date)-first trifluridine/tipiracil intake date]+1)/7)*

Clinical trial exposure for mGC

Phase 3 randomised, placebo controlled mGC study (TO-TAS-102-302/TAGS)

Study Protocol	Number of Patients included (mGC patients receiving 35 mg/m^2/dose of trifluridine-tipiracil or placebo)	Study design and type of control	Included patients
TO-TAS-102-302 [TAGS]	503* (FTD/TPI: 335; placebo: 168) **337 / 170 patients randomized in the FTD/TPI and placebo arms respectively and 335 / 168 received at least one dose of FTD/TPI and placebo resepectively.*	Phase 3, placebo-controlled, multicentre, double-blind, parallel, randomized.	Patients with mGC who had received ≥2 prior regimens of standard chemotherapies (including a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are known to be HER2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available) and were refractory to or unable to tolerate their last prior therapy.

Exposure to study treatment for mGC: cycles, weeks of exposure and cumulative dose

	TAGS FTD/TPI
	(N=335)
Cycles per Subject Initiated [1]	
Total Cycles Initiated	1108
Mean (SD)	3.3 (2.50)
Median	2.0
Min, Max	1 ,14
Weeks [2]	
Total Weeks	4038
Mean (SD)	12.05 (11.467)
Median	6.71
Min, Max	0.4 ,62.7
Cycle initiated [1]	
1	335 (100)
2	282 (84.2)
3	145 (43.3)
4	116 (34.6)
>4	65 (19.4)
Maximum Cycle Initiated [1]	
1	53 (15.8)
2	137 (40.9)
3	29 (8.7)
4	51 (15.2)
5	12 (3.6)
6	23 (6.9)
7	3 (0.9)
8	6 (1.8)
9	5 (1.5)
10	6 (1.8)
11	5 (1.5)
12	3 (0.9)
13	1 (0.3)
14	1 (0.3)

	TAGS FTD/TPI
	(N=335)
16	0
Total Dose Administered (mg/m²)	
n	334
Mean (SD)	2127.332 (1651.7137)
Median	1387.525
Min, Max	104.84,9367.91
Dose Intensity (mg/m²/wk)	
n	334
Mean (SD)	148.201 (26.7921)
Median	156.720
Min, Max	26.21,177.51
Dose Intensity (Ratio to Planned)	
n	334
Mean (SD)	0.847 (0.1531)
Median	0.896
Min, Max	0.15,1.01

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

Exposure by gender for mGC

	TAGS FTD/TPI	
	Male (N=250)	**Female (N=85)**
Cycles per Subject Initiated [1]		
Total Cycles Initiated	808	300
Mean ± SD	3.23±2.45	3.53±2.62
Median	2.00	2.00
Min ; Max	1.0;14.0	1.0;12.0
Weeks [2]		
Total Weeks	2942	1096
Mean ± SD	11.77±11.43	12.89±11.60
Median	6.43	7.57
Min ; Max	0.6;62.7	0.4;48.6

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

Exposure by age for mGC

	TAGS FTD/TPI	
	<65 years (N=182)	**>=65 years (N=153)**
Cycles per Subject Initiated [1]		
Total Cycles Initiated	576	532
Mean ± SD	3.16±2.38	3.48±2.62
Median	2.00	2.00
Min ; Max	1.0;12.0	1.0;14.0
Weeks [2]		
Total Weeks	2049	1988
Mean ± SD	11.26±10.86	13.00±12.12
Median	6.00	7.57
Min ; Max	0.4;52.4	0.7;62.7

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

	TAGS FTD/TPI		
	<65 years (N=182)	**65<= - <75 years (N=103)**	**>=75 years (N=50)**
Cycles per Subject Initiated [1]			
Total Cycles Initiated	576	329	203
Mean ± SD	3.16±2.38	3.19±2.31	4.06±3.13
Median	2.00	2.00	3.00
Min ; Max	1.0;12.0	1.0;12.0	1.0;14.0
Weeks [2]			
Total Weeks	2049	1215	773
Mean ± SD	11.26±10.86	11.80±10.80	15.46±14.27
Median	6.00	6.86	9.64
Min ; Max	0.4;52.4	0.7;48.4	1.1;62.7

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

Exposure by ethnic origin for mGC

	TAGS FTD/TPI				
	White (N=242)	**Asian (N=51)**	**Black or African American (N=1)**	**Other (N=3)**	**Not Collectable (N=38)**
Cycles per Subject Initiated [1]					
Total Cycles Initiated	804	170	4	11	119
Mean ± SD	3.32±2.55	3.33±2.43	4.00±NA	3.67±2.52	3.13±2.32
Median	2.00	2.00	4.00	4.00	2.00
Min ; Max	1.0;14.0	1.0;11.0	4.0;4.0	1.0;6.0	1.0;11.0
Weeks [2]					
Total Weeks	2925	636	14	42	421
Mean ± SD	12.09±11.70	12.47±11.56	13.71±NA	14.05±10.81	11.09±10.33
Median	6.50	6.71	13.71	18.57	6.71
Min ; Max	0.4;62.7	1.7;47.9	13.7;13.7	1.7;21.9	1.6;43.6

[1] Patients counted in each cycle initiated (at least 1 dose of FTD/TPI administered).
[2] (Date of last dose of study medication – date of first dose of study medication +1) / 7
NA: Not Applicable

Exposure by Renal Impairment (baseline creatinine clearance (CLcr) in mGC

	TAGS FTD/TPI			
	Normal >=90 mL/min (N=134)	**Mild Impairment 60-89 mL/min (N=141)**	**Moderate Impairment 30-59 mL/min (N=58)**	**Severe Impairment <30 mL/min (N=2)**
Cycles per Subject Initiated [1]				
Total Cycles Initiated	432	471	197	8
Mean ± SD	3.22±2.40	3.34±2.67	3.40±2.33	4.00±2.83
Median	2.00	2.00	2.50	4.00
Min ; Max	1.0;12.0	1.0;14.0	1.0;10.0	2.0;6.0
Weeks [2]				
Total Weeks	1560	1730	717	30
Mean ± SD	11.64±10.92	12.27±12.41	12.37±10.53	15.21±12.02
Median	6.43	6.71	8.64	15.21
Min ; Max	0.4;48.6	0.7;62.7	0.6;42.7	6.7;23.7

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

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in the pivotal clinical studies RECOURSE (TO-TAS-102-301) and SUNLIGHT (CL3-95005-007) in patients with refractory mCRC and in the pivotal clinical study TAGS (TO-TAS-102-302) in patients with refractory mGC are described hereafter.

Age < 18 years

Reason for exclusion: Not targeted population.

Is it considered to be included as missing information? No.

Rationale: mCRC and mGC are extremely rare in the paediatric population and the Paediatric Committee of the European Medicines Agency (PDCO) has granted a paediatric class waiver for both indications.

Pregnancy, women of childbearing potential without contraception and lactating female.

Reason for exclusion: Precautionary measure due to lack of data in human pregnancy and breast-feeding and in the light of the fact that based on the mechanism of action, trifluridine is suspected to cause congenital malformations when administered during pregnancy. Trifluridine-tipiracil has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure.

Is it considered to be included as missing information? No.

Rationale: As precautionary safety measure, section 4.6 of SmPC mentions that Lonsurf should not be used during pregnancy unless the clinical condition of the woman requires treatment with Lonsurf.

Abnormal bone marrow function (ie neutrophils < 1.5x109/L IU; platelets <100 x109/L IU; haemoglobin < 9 g/dL)

Reason for exclusion: Precautionary safety measure as patients who have a pre-existing anaemia, neutropenia or thrombocytopenia may be at increased risk to develop clinical consequences as a result of bone marrow suppression induced by trifluridine-tipiracil.

Is it considered to be included as missing information? No.

Rationale: Bone marrow suppression is considered as an Important Identified Risk.

Moderate to severe hepatic impairment

Reason for exclusion: Precautionary safety measure.

Is it considered to be included as missing information? No.

Rationale: Based on the results of a Phase 1 study (TO-TAS-102-106) evaluating the use of trifluridine-tipiracil in patients with hepatic impairment, trifluridine-tipiracil is not recommended for use in patients with baseline moderate or severe hepatic impairment.

Severe renal impairment

Reason for exclusion: Precautionary safety measure.

Is it considered to be included as missing information? No.

Rationale: Based on the results of a Phase 1 study (TO-TAS-102-107) evaluating the use of trifluridine-tipiracil in patients with renal impairment, trifluridine-tipiracil could be used in patients with severe renal impairment with adjustement of the starting dose while being more frequently monitored for haematological toxicities.

Concomitant uncontrolled serious illness, medical or psychiatric disease

Reason for exclusion: As the primary objective of the pivotal studies was Overall Survival (OS), these patients were excluded in order to ensure standardization of the study population in order to assess OS.

Is it considered to be included as missing information? No.

Rationale: Acceptable gaps in knowledge about the safety of trifluridine-tipiracil for the population of patients with mCRC and mGC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	No pregnant or breast-feeding women have been exposed to trifluridine-tipiracil in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	A Phase I, open-label study was conducted to evaluate the safety, tolerability, and pharmacokinetics of trifluridine/tipiracil in patients with advanced solid tumours and varying degrees of hepatic impairment (TO-TAS-102-106). A total of 24 patients were enrolled of which 8 patients were enrolled in the normal cohort, 10 patients with mild hepatic impairment, and 6 patients with moderate hepatic impairment. Two patients in the normal cohort experienced ≥ Grade 3 elevated blood bilirubin. Five (all with liver metastasis) of 6 patients in the moderate hepatic impairment cohort experienced blood bilirubin increases of ≥ Grade 3. For 3 of the 5 patients, the investigators considered the ≥ Grade 3 blood bilirubin increase findings to be unrelated to trifluridine/tipiracil, but rather, it was considered that clinical and/or radiologic disease progression caused the elevation but the effect/role of trifluridine/tipiracil on bilirubin elevation could not be completely ruled out. The isolated blood bilirubin elevation findings might be attributed to the combined effect of the 3 contributing confounding factors: liver metastasis status, moderate hepatic impairment status at baseline, as well as the trifluridine/tipiracil. However, because of the high frequency of these isolated increased blood bilirubin findings, it was concluded that patient enrolment with moderate and/or severe hepatic impairment in this study would be discontinued.
• Patients with renal impairment	In the RECOURSE study, 178 (33.3%) patients with mild renal impairment (CLcr60 to 89 mL/min) and 47 (8.8%) patients with moderate renal impairment (CLcr 30 to 59 mL/min) at baseline were exposed to

Type of special population	Exposure
	trifluridine-tipiracil. Patients with severe renal impairment (CLcr <30 mL/min) were not enrolled in the study. In the TAS-102-J003-10040030 clinical study 43 (38.4%) patients with mild renal impairment and 20 (17.8%) patients with moderate renal impairment at baseline were exposed to trifluridine-tipiracil. No patients with severe renal impairment were studied. In the TAGS study, 141 (41.8%) patients with mild renal impairment and 58 (17.2%) patients with moderate renal impairment at baseline were exposed to trifluridine-tipiracil. Patients with severe renal impairment were excluded from the clinical study, however 2 (0.6%) patients with severe renal impairment were enrolled in the trifluridine-tipiracil arm. In the SUNLIGHT study, 168 (34.1%) patients with mild renal impairment and 58 (11.8%) patients with moderate renal impairment at baseline were exposed to trifluridine-tipiracil alone or in combination with bevacizumab. Patients with severe renal impairment were excluded from the clinical study. A phase 1, open-label study was conducted to evaluate the safety, tolerability, and pharmacokinetics of trifluridine-tipiracil in patients with advanced solid tumors and varying degrees of renal impairment (TO-TAS-102-107). A total of 43 patients were enrolled, of which 12 patients in the normal renal function cohort, 12, 11, and 8 patients with mild, moderate, and severe renal impairment (CrCl 15-29 mL/min), respectively. Based on PK and safety data from the normal renal function, mild and moderate renal impairment cohorts, the dose of 20 mg/m2 BID was selected as the starting dose for the severe renal impairment cohort and one dose reduction was allowed to 15 mg/m2 BID in case of toxicities requiring a dose reduction. Renal function impairment had no significant effect on Cmax and AUCs of trifluridine following multiple administration of trifluridine-tipiracil, although tipiracil hydrochloride exposure was increased in patients with renal impairment. Consistent with current knowledge on safety profile of trifluridine-tipiracil moderate renal

Type of special population	Exposure
	impairment patients tended to show a higher incidence of ≥ Grade 3 adverse events and serious adverse events were more frequent in mild and moderate renal impairment patients compared to normal renal function cohort. However, the safety profile in patients with severe renal impairment who received 20 mg/m2/dose twice daily did not show important changes compared to normal renal function and mild renal impairment cohorts demonstrating that a dose of 20 mg/m2 twice daily is appropriate and tolerable for this population of patients. Patients with end stage renal disease (CLcr <15 mL/min or patients requiring dialysis) were not enrolled in the study.
• Patients with cardiovascular impairment	Not included in the clinical development program
• Immunocompromised patients	Not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Population is primarily Caucasian/White and Asian patients. In RECOURSE study, 306 (57.3%) Caucassian/White patients, 184 (34.5%) Asian patients and 4 (0.7%) Black/African american patients were exposed to trifluridine-tipiracil. In addition, within the TAS-102-J003-10040030 clinical study, all patients (ie, 112 patients exposed to trifluridine-tipiracil) were Asian. In TAGS study, 244 (72.4%) Caucasian/White patients, 51 (15.1%) Asian patients and 1 (0.3%) Black/African American patient were exposed to trifluridine-tipiracil. In SUNLIGHT study, 435 (95.2%) Caucasian/White patients, 7 (1.5%) Black/African American patients, 1 (0.2%) American Indian or Alaska patient and 1 (0.2%) Asian patient were exposed to trifluridine-tipiracil alone or in combination with bevacizumab.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Type of special population	**Exposure**
Other: Elderly population	In the RECOURSE study, 234 (43.8%) patients were ≥ 65 years while 7% were 75 and over, exposed to trifluridine-tipiracil. In addition within the TAS-102-J003-10040030 study, 52 (46.4%) patients exposed to trifluridine-tipiracil were ≥ 65 years. In the Group 2 (TAS-102-J003-10040030 and TPU-TAS-102-301) 45 patients were 75 and over, with no patient over the age of 85 years was exposed to trifluridine-tipiracil. In the TAGS study, 154 (45.7%) patients were ≥ 65 years while 15.1% were 75 and over, including 2 patients over the age of 85 years exposed to trifluridine-tipiracil. In the SUNLIGHT study, 217 (44.1%) patients were ≥ 65 years while 11.8% were 75 and over, including 1 patient over the age of 85 years exposed to trifluridine-tipiracil alone or in combination with bevacizumab.

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Data used to estimate the number of patients treated with trifluridine-tipiracil was calculated using the following formula:

Estimated number of patients = (Period sales data x mg) ÷ (120 mg x 10 days) x 3 months.

*120 mg/day of treatment (for an average patient 1.69-1.83 m²) and 10 days of treatment per month (so 1 200 mg per month), and a month of 30.4 days (so a mean of 39.5mg/day).

SV.1.2 Exposure

Based on the formula above, estimated cumulative exposure since first marketing authorization to September 24, 2022 is 289 325 patients.

Table SV.1: Exposure table by region

Region	
EU country	Non EU country
104 974	184 351

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Trifluridine-tipiracil does not have any effects which would make it the subject of abuse or misuse for illegal purposes. Since its MA there is no cases reported of misuse for illegal purposes.

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

In RMP version 8.0, the missing information "Use in patients with severe renal impairment" has been re-classifed as an important identified risk based on final results from study TO-TAS-102-107 and reworded as "Safety in patients with moderate or severe renal impairment".

The following safety concerns have been removed in the updated RMP version 8.0:
- the important identified risk "Bone marrow suppression",
- the important identified risk "Gastrointestinal symptoms (nausea, vomiting and diarrhoea)",
- the important identified risk "Infection",
- the important potential risk "Use in breast-feeding women",
- the missing information "Use in patients with cardiac disorders".

These safety concerns are managed through routine Pharmacovigilance activities including signal detection performed every 3 months, using qualitative and quantitative analysis and through routine risk minimization measures.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Safety in patients with moderate or severe renal impairment

Potential mechanisms:

Renal insufficiency has been shown to be highly prevalent in patients with solid tumors, including mCRC. Renal insufficiency may influence 1 or several of the 4 pharmacokinetic phases (absorption, distribution, metabolism, elimination/excretion), potentially resulting in marked modifications of the pharmacokinetic profile of trifluridine-tipiacil and in a higher incidence of toxicities.

Evidence source(s) and strength of evidence:

Clinical data: Based on a population PK analysis, the exposure of Lonsurf in patients with mild renal impairment (CrCl = 60 to 89 mL/min) was similar to those in patients with normal renal function (CLcr ≥ 90 mL/min). A higher exposure of Lonsurf was observed in moderate renal impairment (CLcr = 30 to 59 mL/min). Estimated (CLcr) was a significant covariate for Oral clearance (CL/F) in both final models of trifluridine and tipiracil hydrochloride. The mean relative ratio of Area Under the Curve (AUC) in patients with mild (n=38) and moderate (n=16) renal impairment compared to patients with normal renal function (n=84) were 1.31 and 1.43 for trifluridine, respectively, and 1.34 and 1.65 for tipiracil hydrochloride, respectively.

During mCRC clinical development it has been shown that patients with moderate renal impairment at baseline had a higher incidence of ≥ Grade 3 Aes and serious Aes, and dose delays and reductions compared to patients with normal renal function or mild renal impairment. In mGC clinical development there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups (based on baseline CLcr) with respect to overall incidence of Aes, ≥ Grade 3 Aes or serious Aes, dose delays and reductions. However, several of the most frequently reported Aes increased with the degree of renal impairment (anaemia, neutropenia, decreased appetite and diarrhoea) and patients with moderate impairment had higher incidences of Grade 3 and 4 abnormalities for haemoglobin and leukocytes compared to normal and mild impairment subgroups.

In a dedicated phase 1, open-label study conducted to evaluate the safety, tolerability, and pharmacokinetics of trifluridine-tipiracil in patients with advanced solid tumors and varying degrees of renal impairment (TO-TAS-102-107), based on PK and safety data from the normal renal function, mild and moderate renal impairment cohorts, a lower starting dose was selected for the severe renal impairment cohort (dose of 20 mg/m2 BID) and one dose reduction was allowed to 15 mg/m2 BID in case of toxicities requiring a dose reduction. Renal function impairment had no significant effect on Cmax and AUCs of trifluridine following multiple administration of trifluridine-tipiracil, although tipiracil hydrochloride exposure was increased in patients with renal impairment. Consistent with current knowledge on safety profile of trifluridine-tipiracil moderate renal impairment patients tended to show a higher incidence of ≥ Grade 3 adverse events and serious adverse events were more frequent in mild and moderate renal impairment patients compared to normal renal function cohort. However, the safety profile in patients with severe renal impairment who received 20 mg/m2/dose twice daily did not show important changes compared to normal renal function and mild renal impairment cohorts demonstrating that a dose of 20 mg/m2 twice daily is appropriate and tolerable for this population of patients. Patients with end stage renal disease (CLcr <15 mL/min or patients requiring dialysis) were not enrolled in the study.

Characterisation of the risk:

Frequency

- *Clinical trials*

Adverse event incidence in mCRC **GROUP 2 according to Baseline CLcr**						
	Normal		**Mild**		**Moderate**	
	FTD/TPI N=356	**Placebo N=179**	**FTD/TPI N=221**	**Placebo N=105**	**FTD/TPI N=67**	**Placebo N=35**
Incidence* N (%)	349 (98)	164 (91.6)	220 (99.5)	100 (95.2)	64 (95.5)	32 (91.4)
95% CI	95.99-99.21	86.56-95.23	97.5-99.99	89.24-98.44	87.47-99.07	76.94-98.20

**Number of patients with at least one AE*

Adverse event incidence in RECOURSE according to Baseline CLcr						
	Normal		**Mild**		**Moderate**	
	FTD/TPI N=306	**Placebo N=146**	**FTD/TPI N=178**	**Placebo N=90**	**FTD/TPI N=47**	**Placebo N=26**
Incidence* N (%)	299 (97.7)	134 (91.8)	177 (99.4)	86 (95.6)	46 (97.9)	24 (92.3)
95% CI	95.34-99.08	86.08-95.68	96.91-99.99	89.01-98.78	88.71-99-95	74.87-99.05

**Number of patients with at least one AE*

Adverse event incidence in SUNLIGHT according to Baseline CLcr			
	Normal	**Mild**	**Moderate**
	FTD/TPI N=265	**FTD/TPI N=168**	**FTD/TPI N=58**
Incidence* N (%)	257 (97.0)	166 (98.8)	58 (100.0)
95% CI	94.14-98.69	95.77-99.86	93.84-100.00

**Number of patients with at least one AE*

Adverse event incidence in TAGS according to Baseline CLcr								
	Normal		**Mild**		**Moderate**		**Severe**	
	FTD/TPI N=134	**Placebo N=68**	**FTD/TPI N=141**	**Placebo N=71**	**FTD/TPI N=58**	**Placebo N=28**	**FTD/TPI N=2**	**Placebo N=1**
Incidence* N (%)	131 (97.8)	65 (95.6)	137 (97.2)	63 (88.7)	56 (96.6)	28 (100.0)	2 (100.0)	1 (100.0)
95% CI	93.60-99.54	87.64-99.08	92.90-99.22	79.00-95.01	88.09-99.58	87.66-100.00	15.81-100.00	2.50-100.00

**Number of patients with at least one AE*

No relevant difference was observed in the incidence of AEs among renal function categories in both arms of Group 2, RECOURSE and TAGS.

In the SUNLIGHT study, no difference was observed in the incidence of AEs among the renal functions categories.

However, in the TAGS study, among patient exposed to trifluridine-tipiracil, the incidence of several of the most frequently reported (≥ 25% of patients) adverse events increased with the degree of renal impairment. The incidences for the normal renal function, mild renal impairment and moderate renal impairment categories were 38.8%, 41.8% and 63.8%, respectively for anemia; 34.3%, 41.1% and 43.1% for neutropenia; 27.6%, 39.0%, and 37.9% for decreased appetite; and 20.9%, 22.7% and 25.9% for diarrhea. In the placebo arm, the corresponding incidence followed similar trends but at generally lower rates.

In the trifluridine-tipiracil group of mCRC Group 2, the incidence of the most frequently reported (≥25% of patients) non-haematological Aes did not appear to increase in proportion to the degree of renal impairment (normal renal function, mild and moderate renal impairment) except for diarrhoea (31.5%, 33.0%, 41.8% respectively) and fatigue (37.9%, 35.3%, 46.3% respectively).

In the dedicated Phase 1 study (TO-TAS-102-107), 43 patients were enrolled, of which 12 patients in the normal renal function cohort, 12, 11, and 8 patients with mild, moderate, and severe renal impairment, respectively and no difference was observed in the incidence of Aes among renal function categories. All patients (100%) from each cohort (normal, mild, moderate, severe renal impairment) experienced at least one AE and the incidences of Aes by preferred term did not increase with decreasing renal function. The most frequently reported preferred terms overall (≥ 25%) were fatigue (55.8%), nausea, decreased appetite (48.8%), anemia (39.5%), vomiting (34.9%), dehydration (27.9%), diarrhea, dyspnea (25.6%).

- *Post marketing data*

Cumulatively, since MA up to 24 September 2022, 256 cases with a medical history of renal dysfunction have been received, representing an estimated reporting rate of 88/100 000 patients.

Severity

- *Clinical trials*

Severity of Adverse events in mCRC **GROUP 2 according to Baseline CLcr**						
Grade* N (%)	**Normal**		**Mild**		**Moderate**	
	FTD/TPI N=356	**Placebo N=179**	**FTD/TPI N=221**	**Placebo N=105**	**FTD/TPI N=67**	**Placebo N= 35**
5	7 (2.0)	18 (10.1)	8 (3.6)	9 (8.6)	3 (4.5)	2 (5.7)
4	49 (13.8)	11 (6.1)	44 (19.9)	6 (5.7)	23 (34.3)	3 (8.6)
3	182 (51.1)	50 (27.9)	106 (48.0)	34 (32.4)	26 (38.8)	12 (34.3)
2	91 (25.6)	52 (29.1)	51 (23.1)	33 (31.4)	10 (14.9)	8 (22.9)
1	20 (5.6)	33 (18.4)	11 (5.0)	18 (17.1)	2 (3.0)	7 (20.0)

**Severity categories are summarized by worst occurring result per patient*

Severity of Adverse events in RECOURSE according to Baseline CLcr						
Grade* N (%)	**Normal**		**Mild**		**Moderate**	
	FTD/TPI N=306	**Placebo N=146**	**FTD/TPI N=178**	**Placebo N=90**	**FTD/TPI N=47**	**Placebo N= 26**
5	7 (2.3)	18 (12.3)	7 (3.9)	9 (10.0)	3 (6.4)	2 (7.7)
4	42 (13.7)	9 (6.2)	32 (18.0)	5 (5.6)	15 (31.9)	2 (7.7)
3	155 (50.7)	48 (32.9)	87 (48.9)	33 (36.7)	22 (46.8)	10 (38.5)
2	78 (25.5)	35 (24.0)	42(23.6)	24 (26.7)	5 (10.6)	4 (15.4)
1	17 (5.6)	24 (16.4)	9 (5.1)	15 (16.7)	1 (2.1)	6 (23.1)

**Severity categories are summarized by worst occurring result per patient*

Severity of Adverse events in SUNLIGHT according to Baseline CLcr			
Grade* N (%)	**Normal**	**Mild**	**Moderate**
	FTD/TPI N=265	**FTD/TPI N=168**	**FTD/TPI N=58**
5	22 (8.30)	7 (4.17)	4 (6.90)
4	38 (14.34)	38 (22.62)	8 (13.79)
3	112 (42.26)	84 (50.00)	35 (60.34)
2	72 (27.17)	32 (19.05)	10 (17.24)
1	13 (4.91)	5 (2.98)	1 (1.72)

**Severity categories are summarized by worst occurring result per patient*

Severity of Adverse events in TAGS according to Baseline CLcr								
Grade* N (%)	**Normal**		**Mild**		**Moderate**		**Severe**	
	FTD/TPI N=134	**Placebo N=68**	**FTD/TPI N=141**	**Placebo N=71**	**FTD/TPI N=58**	**Placebo N=28**	**FTD/TPI N=2**	**Placebo N=1**
5	19 (14.2)	9 (13.2)	23 (16.3)	7 (9.9)	2 (3.4)	3 (10.7)	0 (0.0)	0 (0.0)
4	16 (11.9)	8 (11.8)	22 (15.6)	3 (4.2)	11 (19.0)	2 (7.1)	2 (100.0)	1 (100.0)
3	64 (47.8)	27 (39.7)	74 (52.5)	28 (39.4)	34 (58.6)	9 (32.1)	0 (0.0)	0 (0.0)
2	30 (22.4)	16 (23.5)	15 (10.6)	16 (22.5)	8 (13.8)	7 (25.0)	0 (0.0)	0 (0.0)
1	2 (1.5)	5 (7.4)	3 (2.1)	9 (12.7)	1 (1.7)	7 (25.0)	0 (0.0)	0 (0.0)

**Severity categories are summarized by worst occurring result per patient*

In mCRC Group 2 and RECOURSE, patients with moderate renal impairment had a higher incidence (defined as a difference of at least 5%) of ≥ Grade 3 Aes compared to the normal and mild renal impairment subgroups. These trends were less apparent among patients in the placebo group. In the trifluridine-tipiracil arm of mCRC Group 2, frequencies of the following Grade 3 or 4 haematological abnormalities increased with degree of renal impairment (normal renal function, mild and moderate renal impairment): low haemoglobin (11.6%, 20.9%, 47.0% respectively), low lymphocyte count (15.7%, 22.7%, 34.8%), low neutrophil count (36.5%, 44.1%, 47%), and low white blood cell count (19.8%, 24.5%, 31.8%). Frequencies of these abnormalities in the placebo group showed no consistent pattern across renal impairment categories.

In SUNLIGHT, patients with mild or moderate renal impairment had a higher incidence (defined as a difference of at least 5%) of ≥ Grade 3 AEs compared to patients with the normal renal function.

In the TAGS study, no relevant difference was observed in the incidence of ≥ Grade 3 adverse events among renal function categories. In terms of Grade 3 or 4 hematologic abnormalities, no

trends were observed for patients with normal renal function and patients with mild impairment; however, for patients with moderate impairment, higher incidences of Grade 3 and 4 abnormalities were observed for hemoglobin (decrease) and leukocytes (decrease).

Patients with moderate renal impairment at baseline had a higher incidence of dose delays, drug interruption and dose reduction. Among patients in Group 2 receiving trifluridine-tipiracil:

- the incidence of dose reductions in the normal, mild, and moderate renal impairment groups was 11.2%, 17.6%, and 23.9%, respectively. Only 3 patients in the placebo group had dose reductions.
- the incidence of drug interruption in normal, mild, and moderate groups was 28.7%, 26.7%, and 38.8%, respectively.
- cycle initiation delays of ≥8 days were observed in 22.0% of patients with normal renal function, 31.8% with mild renal impairment, and 35.3% with moderate renal impairment. Only 9 patients in the placebo group had cycle initiation delays of ≥8 days.

In the dedicated Phase 1 study (TO-TAS-102-107), grade 3 or higher Aes affected more frequently patients with renal function impairment than those with normal renal function, with the highest incidence observed in the moderate cohort (normal: 50.0%, mild: 83.3%, moderate: 90.9%, severe: 75.0%).

Severity of Adverse events in TO-TAS-102-107 according to Baseline CLcr				
Grade* N (%)	**Normal**	**Mild**	**Moderate**	**Severe**
	FTD/TPI N=12	**FTD/TPI N=12**	**FTD/TPI N=11**	**FTD/TPI N=8**
5	0.0	0.0	0.0	0.0
4	3 (25.0)	5 (41.7)	2 (18.2)	0.0
3	3 (25.0)	5 (41.7)	8 (72.7)	6 (75.0)
2	5 (41.7)	2 (16.7)	1 (9.1)	2 (25.0)
1	1 (8.3)	0.0	0.0	0.0

**Severity categories are summarized by worst occurring result per patient*

- *Post marketing data*

The severity of events is rarely mentioned in post-marketing case reports. The table below summarizes the severity (as assessed by the reporter) of the 25 events reported in patients with medical history of moderate renal impairment during the Servier CUP since MA up to 24 September 2022. The severity has been classified according to CTCAE criteria (v4.03).

Preferred Term	Outcome					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Not reported**	**Total**
Anaemia		2	2			4
Bronchitis			1			1
Diarrhoea		2	1			3
Febrile neutropenia					1	1
Leukopenia			1		1	2
Musculoskeletal pain					1	1
Neutropenia	1	1	2	2		6
Neutropenic sepsis			1			1
Pneumonia					1	1
Prescribed underdose					1	1
Pyrexia		1				1
Sepsis					1	1
Soft tissue infection					1	1
Thrombocytopenia			1			1
Total	**1**	**6**	**9**	**2**	**7**	**25**

Seriousness/outcomes

- *Clinical trials*

Seriousness of Adverse events in mCRC GROUP 2 according to Baseline CLcr						
Seriousness (1) N (%)	**Normal**		**Mild**		**Moderate**	
	FTD/TPI N=356	**Placebo N=179**	**FTD/TPI N=221**	**Placebo N=105**	**FTD/TPI N=67**	**Placebo N=35**
Serious	90 (25.3)	47 (26.3)	63 (28.5)	37 (35.2)	26 (38.8)	9 (25.7)
Non serious	259 (72.8)	117 (65.4)	157 (71.0)	63 (60.0)	38 (56.7)	23 (65.7)

(1) Seriousness is summarized by worst occurring result per patient

Seriousness of Adverse events in RECOURSE according to Baseline CLcr						
Seriousness (1) N (%)	**Normal**		**Mild**		**Moderate**	
	FTD/TPI N=306	**Placebo N=146**	**FTD/TPI N=178**	**Placebo N=90**	**FTD/TPI N=47**	**Placebo N=26**
Serious	84 (27.5)	44 (30.1)	54 (30.3)	36 (40)	20 (42.6)	8 (30.8)
Non serious	215 (70.3)	90 (61.6)	123 (69.1)	50 (55.6)	26 (55.3)	16 (61.5)

(1) Seriousness is summarized by worst occurring result per patient

Seriousness of Adverse events in SUNLIGHT according to Baseline CLcr			
Grade* N (%)	**Normal**	**Mild**	**Moderate**
	FTD/TPI N=265	**FTD/TPI N=168**	**FTD/TPI N=58**
Serious	66 (24.9)	52 (31.0)	20 (34.5)
Non serious	191 (72.1)	114 (67.9)	38 (65.5)

(1) Seriousness is summarized by worst occurring result per patient

Seriousness of Adverse events TAGS according to Baseline CLcr								
Seriousness (1) N (%)	**Normal**		**Mild**		**Moderate**		**Severe**	
	FTD/TPI N=134	**Placebo N=68**	**FTD/TPI N=141**	**Placebo N=71**	**FTD/TPI N=58**	**Placebo N=28**	**FTD/TPI N=2**	**Placebo N=1**
Serious	62 (46.3)	34 (50.0)	58 (41.1)	26 (36.6)	22 (37.9)	9 (32.1)	1 (50.0)	1 (100.0)
Non serious	69 (51.5)	31 (45.6)	79 (56.0)	37 (52.1)	34 (58.6)	19 (67.9)	1 (50.0)	0 (0.0)

(1) Seriousness is summarized by worst occurring result per patient

Outcome of Adverse events in mCRC **GROUP 2 according to Baseline CLcr**						
Outcomes (1) N (%)	**Normal**		**Mild**		**Moderate**	
	FTD/TPI N=356	**Placebo N=179**	**FTD/TPI N=221**	**Placebo N=105**	**FTD/TPI N=67**	**Placebo N=35**
Fatal	7 (2.0)	18 (10.1)	8 (3.6)	9 (8.6)	3 (4.5)	2 (5.7)
Unknown	32 (9.0)	17 (9.5)	35 (15.8)	5 (4.8)	10 (14.9)	6 (17.1)
Not recovered/Not resolved	261 (73.3)	111 (62.0)	152 (68.8)	73 (69.5)	48 (71.6)	21 (60)
Recovered/resolved with sequalae	1 (0.3)	1 (0.6)	0	0	0	0
Recovered/resolved	48 (13.5)	17 (9.5)	25 (11.3)	13 (12.4)	3 (4.5)	3 (8.6)
Recovering/resolving	0	0	0	0	0	0

(1) Outcome categories are summarized by worst occurring result per patient

Outcome of Adverse events in RECOURSE according to Baseline CLcr						
Outcomes (1) N (%)	Normal		Mild		Moderate	
	FTD/TPI N=306	**Placebo N=146**	**FTD/TPI N=178**	**Placebo N=90**	**FTD/TPI N=47**	**Placebo N=26**
Fatal	7 (2.3)	18 (12.3)	7 (3.9)	9 (10.0)	3 (6.4)	2 (7.7)
Unknown	0	0	0	0	0	0

Outcome of Adverse events in RECOURSE according to Baseline CLcr						
Not recovered/Not resolved	246 (80.4)	100 (68.5)	146 (82.0)	67 (74.4)	42 (89.4)	20 (76.9)
Recovered/resolved with sequalae	1 (0.3)	1 (0.7)	0	0	0	0
Recovered/resolved	45 (14.7)	15 (10.3)	24 (13.5)	10 (11.1)	1 (2.1)	2 (7.7)
Recovering/resolving	0	0	0	0	0	0

(1) Outcome categories are summarized by worst occurring result per patient

Outcome of Adverse events SUNLIGHT according to Baseline CLcr			
Outcomes (1) N (%)	**Normal**	**Mild**	**Moderate**
	FTD/TPI N=265	**FTD/TPI N=168**	**FTD/TPI N=58**
Fatal	26 (9.81)	10 (5.95)	4 (6.90)
Unknown	0 (0.0)	0 (0.0)	1 (1.72)
Not recovered/Not resolved	146 (55.09)	110 (65.48)	48 (82.76)
Recovering/resolving	14 (5.28)	9 (5.36)	0 (0.0)
Recovered/resolved with sequalae	0 (0.0)	1 (0.60)	0 (0.0)
Recovered/resolved	71 (26.79)	36 (21.43)	5 (8.62)

(1) Outcome categories are summarized by worst occurring result per patient

Outcome of Adverse events TAGS according to Baseline CLcr								
Outcomes (1) N (%)	**Normal**		**Mild**		**Moderate**		**Severe**	
	FTD/TPI N=134	**Placebo N=68**	**FTD/TPI N=141**	**Placebo N=71**	**FTD/TPI N=58**	**Placebo N=28**	**FTD/TPI N=2**	**Placebo N=1**
Fatal	19 (14.2)	9 (13.2)	24 (17.0)	7 (9.9)	2 (3.4)	3 (10.7)	0 (0.0)	0 (0.0)
Unknown	7 (5.2)	2 (2.9)	5 (3.5)	2 (2.8)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)
Not recovered/ Not resolved	91 (67.9)	50 (73.5)	88 (62.4)	47 (66.2)	50 (86.2)	21 (75.0)	1 (50.0)	1 (100.0)
Recovering/ resolving	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Outcome of Adverse events TAGS according to Baseline CLcr								
Outcomes (1) N (%)	**Normal**		**Mild**		**Moderate**		**Severe**	
	FTD/TPI N=134	**Placebo N=68**	**FTD/TPI N=141**	**Placebo N=71**	**FTD/TPI N=58**	**Placebo N=28**	**FTD/TPI N=2**	**Placebo N=1**
Recovered/resolved with sequalae	1 (0.7)	0 (0.0)	3 (2.1)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Recovered/resolved	13 (9.7)	4 (5.9)	17 (12.1)	6 (8.5)	4 (6.9)	3 (10.7)	1 (50.0)	0 (0.0)

(1) *Outcome categories are summarized by worst occurring result per patient*

In the Groupe 2, RECOURSE study, patients with moderate renal impairment had a higher incidence of serious Aes, compared to the patients with normal or mild renal impairment.

In the SUNLIGHT study, patients with moderate and mild renal impairment had a higher incidence of serious AEs, compared to the patients with normal renal function.

In TAGS, there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups with respect to overall incidence of serious Aes.

In the dedicated Phase 1 study (TO-TAS-102-107), serious Aes affected more frequently patients from the mild and moderate cohorts (58.3% and 45.5%) compared to the normal cohort (33.3%). Patients with severe renal impairment and adjusted starting dose did not show meaningful changes regarding serious Aes compared with patients with normal renal function (37.5% versus 33.3%). No deaths occurred during the study.

- *Post marketing data*

Cumulatively, since MA up to 24 September 2022, 948 events (in 256 patients) were reported with medical history of renal impairment, including 231 serious events. The outcome of these events is presented in the table below:

Outcome of adverse events since MA in patients with medical history of renal impairment	
Outcomes	**N (%)**
Fatal	35 (3.7)
Unknown	427 (45)
Not recovered	241 (25.4)
Recovered	189 (20)
Recovering	56 (5.9)
Total	**948 (100)**

Impact on quality of life

The impact on the individual mCRC patient with moderate renal impairment is that there is an increased risk of ≥ grade 3 Aes, serious Aes, dose delays and reductions compared to patients with mild renal impairment or normal renal function. In mGC patients, there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups with respect to overall incidence of Aes, ≥ Grade 3 Aes or serious Aes, dose delays

and reductions. However, several of the most frequently reported Aes increased with the degree of renal impairment (anaemia, neutropenia, decreased appetite and diarrhoea) and patients with moderate impairment had higher incidences of Grade 3 and 4 abnormalities for haemoglobin and leukocytes compared to normal and mild impairment subgroups.

Risk factors and risk groups:

Not applicable.

Preventability:

Patients with moderate or severe renal impairment should be more frequently monitored for haematological toxicities.

For patients with severe renal impairment, it is recommended to start treatment with 20 mg/m^2 BID and to reduce the dose to 15 mg/m^2 BID in case of toxicities requiring a dose reduction.

Impact on the risk-benefit balance of the product:

Based on the information from clinical studies and post-marketing experience, no changes regarding the risk-benefit balance of the product in patients with moderate renal impairment has been detected.

Public health impact:

There is minimal public health impact.

Important Potential Risk: Developmental toxicity/Use in pregnant women

Potential mechanisms:

FTD is an antineoplastic agent whose mechanism of action is to inhibit cell growth and cell division. Therefore trifluridine is suspected to cause congenital malformations when administered during pregnancy.

Evidence source(s) and strength of evidence:

Non-clinical data: Based on finding in animals, Lonsurf has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure.

Pregnancy, women of childbearing potential without contraception were not enrolled in the clinical development of Lonsurf.

Characterisation of the risk:

Frequency

- *Clinical trials*

Not applicable.

- *Post marketing experience*

Since the first MA up to 24 September 2022, 3 reports of pregnancy have been reported, representing a reporting rate of 1/100 000 patients.

Severity

Not applicable.

Seriousness/outcomes

There are 3 cases of pregnancies associated with use of trifluridine-tipiracil:

- One case concern indirect cutaneous exposure in the 3rd trimester (a women may had indirect contact with trifluridine-tipiracil via counter-top which her father who was treated with trifluridine-tipiracil had put the product, S17001285).
- One is a case of paternal exposure (a women had sexual relation with a patient treated with trifluridine-tipiracil at cycle 2 day 22 or 23 and she got pregnant, S17002652).
- One is a case of paternal exposure (a pharmacist called as a male patient treated with Lonsurf got his partner pregnant few weeks after first Lonsurf intake, S18000026).

Impact on quality of life

The impact of use of trifluridine-tipiracil in pregnancy on the infant is unknown as there is no data in humans; however, animal studies showed developmental toxicity during pregnancy.

Risk factors and risk groups:

Not applicable.

Preventability:

Women of childbearing potential should avoid becoming pregnant while taking trifluridine-tipiracil and for up to 6 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking Lonsurf and for 6 months after stopping treatment. It is currently unknown whether trifluridine-tipiracil may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier contraceptive method.

Men with a partner of child-bearing potential must use effective contraception during treatment and for up to 6 months after discontinuation of treatment.

Trifluridine-tipiracil should not be used during pregnancy unless the clinical condition of the woman requires treatment with trifluridine-tipiracil.

Impact on the risk-benefit balance of the product:

The use in pregnant women has a minimal impact on the risk-benefit balance of the product since trifluridine-tipiracil should not be used during pregnancy.

Public health impact:

Unknown.

SVII.3.2. Presentation of the missing information

Missing information: Use in patients in worse condition than ECOG 0-1.

Evidence source:
In the RECOURSE, the SUNLIGHT and the TAGS studies, patients with an Eastern Cooperative Oncology Group (ECOG) score ≥2 were excluded and in J003-10040030 only 3 patients (3%) were randomized into the trifluridine-tipiracil group. Nevertheless, it is foreseeable that Lonsurf can be used in patients with ECOG score ≥2; those patients are morefrail and it could be expected that they would be less tolerant to Lonsurf as compared to those who have better ECOG score.

Population in need of further characterisation:
No new safety insight was detected regarding the use in patients in a worse condition than ECOG 0-1 in the post-marketing cumulative review. However due to the nature of post-marketing cases, limited information was provided regarding ECOG performance status (ECOG PS) history, therefore further characterisation of patients in a worse condition than ECOG 0-1 is needed.

Part II: Module SVIII – Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Safety in patients with moderate or severe renal impairment
Important potential risks	Developmental toxicity/Use in pregnant women
Missing information	Use in patients in worse condition than ECOG 0-1.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The important identified risks and important potential risks are well characterised. Therefore, routine pharmacovigilance activities including signal detection are deemed sufficient.

III.2 Additional pharmacovigilance activities

PASS DIM-95005-001 (PROMETCO) summary

Study short name and title:

DIM-95005-001 (PROMETCO) – A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective.

Rationale and study objectives:

Rational: The use of Lonsurf in cancer patients with an ECOG performance status of ≥2 has not been studied.

Study objectives: To provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions. The study might further characterise the safety profile of Lonsurf with respect to the area of missing information "Use in patients in worse condition than ECOG 0-1".

Study design:

Non-interventional prospective cohort study.

Study population:

- Male and female patients, age 18 years or older,
- Diagnosis of mCRC,
- Having had two disease progressions since diagnosis of first metastasis that led to first systemic treatment,
- Willing to receive subsequent treatment.

Milestones:

Final report submission: December 2024.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				
DIM-95005-001 (PROMETCO-EUPAS33865) – A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective On-going	Provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions. The study might further characterise the safety profile of Lonsurf with respect to the area of missing information "Use in patients in worse condition than ECOG 0-1".	Use in patients in a worse condition than ECOG 0-1	Final report	December 2024

Part IV: Plans for post-authorisation efficacy studies
Not applicable

Part V: Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Safety in patients with moderate or severe renal impairment	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: • Dose adjustments information is included in SmPC section 4.2 • Warning on serious adverse events, exposure of trifluridine and tipiracil and recommended haematological toxicities monitoring are provided in SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products

Safety concern	Routine risk minimisation activities
Developmental toxicity/Use in pregnant women	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warnings on the use of Lonsurf during pregnancy, and fertility period are provided in SmPC section 4.6 • Recommandations on pregnancy and contraception are provided in PL section 2 Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products
Use in patients in a worse condition than ECOG 0-1	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: None

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and riks minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Safety in patients with moderate or severe renal impairment.	Routine risk minimisation measures: SmPC sections 4.2 , 4.4 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Developmental toxicity/Use in pregnant women	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients in a worse condition than ECOG 0-1	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Study DIM-95005-001 (PROMETCO)

Part VI: Summary of the risk management plan

Summary of risk management plan for Lonsurf (trifluridine and tipiracil)

This is a summary of the risk management plan (RMP) for Lonsurf. The RMP details important risks of Lonsurf, how these risks can be minimised, and how more information will be obtained about Lonsurf's risks and uncertainties (missing information).

Lonsurf's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Lonsurf should be used.

This summary of the RMP for Lonsurf should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Lonsurf 's RMP.

I. The medicine and what it is used for

Lonsurf is authorised in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents, as monotherapy for the treatment of adult patients with metastatic colorectal cancer 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 and the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease (see SmPC for the full indication). It contains trifluridine and tipiracil (as hydrochloride) as the active substances and it is given by oral administration.

Further information about the evaluation of Lonsurf's benefits can be found in Lonsurf's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/lonsurf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lonsurf, together with measures to minimise such risks and the proposed studies for learning more about Lonsurf's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of Lonsurf is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lonsurf are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lonsurf. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long- term use of the medicine).

List of important risks and missing information	
Important identified risks	Safety in patients with moderate or severe renal impairment
Important potential risks	Developmental toxicity/Use in pregnant women
Missing information	Use in patients in a worse condition than ECOG 0-1.

II.B Summary of important risks

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
Evidence for linking the risk to the medicine	**Clinical data**: Based on a population PK analysis, the exposure of Lonsurf in patients with mild renal impairment (CLcr= 60 to 89 mL/min) was similar to those in patients with normal renal function (CLcr ≥ 90 mL/min). A higher exposure of Lonsurf was observed in moderate renal impairment (CLcr = 30 to 59 mL/min). Estimated (CLcr)

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
	was a significant covariate for Oral clearance (CL/F) in both final models of trifluridine and tipiracil hydrochloride. The mean relative ratio of Area Under the Curve (AUC) in patients with mild (n=38) and moderate (n=16) renal impairment compared to patients with normal renal function (n=84) were 1.31 and 1.43 for trifluridine, respectively, and 1.34 and 1.65 for tipiracil hydrochloride, respectively. During mCRC clinical development it has been shown that patients with moderate renal impairment at baseline had a higher incidence of ≥ Grade 3 Aes and serious Aes, and dose delays and reductions compared to patients with normal renal function or mild renal impairment. In mGC clinical development there was no marked difference between the normal renal function, the mild and the moderate renal impairment subgroups (based on baseline CLcr) with respect to overall incidence of Aes, ≥ Grade 3 Aes or serious Aes, dose delays and reductions. However, several of the most frequently reported Aes increased with the degree of renal impairment (anaemia, neutropenia, decreased appetite and diarrhoea) and patients with moderate impairment had higher incidences of Grade 3 and 4 abnormalities for haemoglobin and leukocytes compared to normal and mild impairment subgroups. In a dedicated phase 1, open-label study conducted to evaluate the safety, tolerability, and pharmacokinetics of trifluridine-tipiracil in patients with advanced solid tumors and varying degrees of renal impairment (TO-TAS-102-107), based on PK and safety data from the normal renal function, mild and moderate renal impairment cohorts, a lower starting dose was selected for the severe renal impairment cohort (dose of 20 mg/m2 BID) and one dose reduction was allowed to 15 mg/m2 BID in case of toxicities requiring a dose reduction. Renal function impairment had no significant effect on Cmax and AUCs of trifluridine following multiple administration of trifluridine-tipiracil, although tipiracil hydrochloride exposure was increased in patients with renal impairment. Consistent with current knowledge on safety profile of trifluridine-tipiracil moderate renal impairment patients tended to show a higher incidence of ≥ Grade 3 adverse events and serious adverse events were more frequent in mild and moderate renal impairment patients compared to normal renal function cohort. However, the

Important Identified Risk: Safety in patients with moderate or severe renal impairment	
	safety profile in patients with severe renal impairment who received 20 mg/m2/dose twice daily did not show important changes compared to normal renal function and mild renal impairment cohorts demonstrating that a dose of 20 mg/m2 twice daily is appropriate and tolerable for this population of patients. Patients with end stage renal disease (CLcr <15 mL/min or patients requiring dialysis) were not enrolled in the study.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 , 4.4 Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important Potential Risk: Developmental toxicity/ Use in pregnant women	
Evidence for linking the risk to the medicine	**Non-clinical data**: Based on finding in animals, Lonsurf has been shown to cause embryo-foetal lethality and embryo-foetal toxicity in pregnant rats when given at dose levels lower than the clinical exposure. Pregnancy, women of childbearing potential without contraception were not enrolled in the clinical development of Lonsurf.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status: Prescription only medicine. Lonsurf should only be prescribed by a qualified physician experienced in treating cancer patients with anti-neoplastic medicinal products. Additional risk minimisation measures: None

Missing information: Use in patients in a worse condition than ECOG 0-1	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study DIM-95005-001 (PROMETCO)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lonsurf.

II.C.2 Other studies in post-authorisation development plan

DIM-95005-001 (PROMETCO) – A Real World Evidence Prospective Cohort Study in the Management of Metastatic Colorectal Cancer: A Clinical and Patient Perspective

Purpose of the study:

Rational: The use of Lonsurf in cancer patients with an ECOG performance status of ≥2 has not been studied.

Study objectives: To provide real world data on treatment patterns, associated effectiveness and safety, and impact on patients with mCRC after two disease progressions. The study might further characterise the safety profile of Lonsurf with respect to the area of missing information "Use in patients in worse condition than ECOG 0-1".

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

None.

Annex 6 – Details of proposed additional risk minimisation activities

Not applicable.