

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207981Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

<b>Clinical Pharmacology NDA Review</b>	
NDA/SDN	NDA 207981 <a href="\\cdsesub1\evsprod\nda207981\207981.enx">\\cdsesub1\evsprod\nda207981\207981.enx</a>
Submission Date (Rolling)	10/16/14, 11/7/14 and 12/19/14
Type/Category	NME, original NDA (Standard)
	Fast track designation
Brand (generic) Name	Lonsurf (TAS-102), combination product of trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5 (weight ratio, 1:0.471)
Dosage Form /Strength	Tablets ( 15 and 20 mg)
Dosing Regimen	35 mg/m <sup>2</sup> /dose (based on trifluridine), twice daily (BID) for 5 days a week with 2 days rest for 2 weeks, followed by a 2 weeks rest, repeated every 4 weeks
Proposed Indication	Metastatic colorectal cancer (CRC)
Applicant	Taiho Oncology, Inc.
OND Division	Division of Oncology Products 2 (DOP2)
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
OCP reviewers	Xianhua (Walt) Cao, Ph.D. (DCPV) Jingyu (Jerry) Yu, Ph.D. (DPM)
OCP Team Leaders/Secondary Reviewers	Hong Zhao, Ph.D. (DCPV) Yaning Wang, Ph.D. (DPM)
PDUFA Goal Date	December 19, 2015

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## 1 EXECUTIVE SUMMARY

A new molecular entity (NME) NDA for Lonsurf (combination of trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5) is submitted for treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy. The proposed dosage regimen of Lonsurf is 35 mg/m<sup>2</sup>/dose (based on trifluridine) administered orally twice daily (BID), within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, repeated in each 28 day cycle until disease progression or unacceptable toxicity.

The efficacy and safety of Lonsurf was established in a randomized (2:1), placebo-controlled, double blinded trial in patients with mCRC who had received  $\geq 2$  prior regimens of standard chemotherapies and were refractory to or failing those chemotherapies. Addition of Lonsurf to best supportive care (BSC) resulted in a clinically meaningful and statistically significant improvement in overall survival (OS) of 1.8 months (7.1 versus 5.3 months, HR 0.68 [95% CI: 0.58, 0.81]) and progression-free survival (PFS) of 0.3 months (2.0 versus 1.7 months, HR 0.48 [95% CI: 0.40, 0.55]) as compared to placebo plus BSC. The most common adverse drug reactions or laboratory abnormalities (all Grades and  $\geq 10\%$  in incidence) in patients treated with Lonsurf at a rate that exceeds the rate in patients receiving placebo plus BSC were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

The Clinical Pharmacology program in the NDA includes studies of dose finding, contribution of the PK modulator component (tipiracil), food effect, cardiac safety, ADME (absorption, distribution, metabolism, excretion), and relative bioavailability in patients with cancer. Population pharmacokinetic (PopPK) analyses using data from 239 patients administered with the proposed dosage regimen identified that body size and renal function are the primary intrinsic factors affecting the exposure to trifluridine and tipiracil. The proposed body surface area (BSA) based dosing is justified. Exploratory exposure-response (E-R) analyses were inconclusive as the PK data were available in only 26% (138/534) of the Lonsurf treated patients in the registrational study. No evident E-R relationships for efficacy (OS) or for adverse reactions could be identified based on the analysis of the limited data.

The proposed dosing regimen of 35 mg/m<sup>2</sup>/dose orally BID for 5 days a week with 2 days rest for 2 weeks, repeated in each 28 day cycle is acceptable.

### 1.1 RECOMMENDATIONS

NDA 207981 is acceptable for approval from a clinical pharmacology perspective provided that the Applicant and FDA come to an agreement regarding the labeling language and completion of the ongoing clinical pharmacology trials under postmarketing requirements (PMRs). The adequacy of the clinical pharmacology program in the overall drug development plan of Lonsurf is summarized in the table below.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 35 mg/m <sup>2</sup> /dose BID, for 5 days a week for 2 weeks, repeated in each 28 day cycle	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  Refer to <a href="#">Section 2.2.4.4</a> and <a href="#">2.5.3</a>	<b>Labeling Recommendation:</b> The recommended dose is 35 mg/m <sup>2</sup> BID within one hour of completion of morning and evening meals on Days 1- 5 and Days 8 -12 of each 28-day cycle until disease progression or unacceptable toxicity.
(b) (4)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  Refer to <a href="#">Section 2.3.1.5</a> and <a href="#">2.3.1.6</a>	<b>Labeling Recommendation:</b> Dose adjustment is not recommended in patients with mild hepatic impairment, and mild to moderate renal impairment. The pharmacokinetics of Lonsurf has not been studied in patients with moderate to severe hepatic impairment, and patients with severe renal impairment.  <b>PMRs:</b> Hepatic and renal impairment studies. Refer to <a href="#">Section 1.2.1</a> .
Dose adjustment in patients with comedications that affect the PK of Lonsurf	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  Refer to <a href="#">Section 2.4.2</a>	<b>Comment:</b> No dose adjustment is recommended. trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Concomitant administration of OCT2 inhibitor had no clinically meaningful effect on exposure to trifluridine or tipiracil
Proposed commercial tablet formulation	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  Refer to <a href="#">Section 2.5.2</a>	<b>Comment:</b> The proposed commercial tablet formulation is identical to the Late Clinical Trial Material (CTM) formulation with the exception of imprinting, which was used in the registration trial (Study RE COURSE).

## 1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

### 1.2.1 Post Marketing Requirements (PMR)

The Applicant is required to complete the following clinical pharmacology trials under the PMR provision. The PMR trials will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

<b>Drug Development Question</b>	<b>Rational</b>	<b>PMR</b>
Should the dose of Lonsurf be modified in patients with moderate or severe hepatic impairment?	The active component trifluridine (FTD) in Lonsurf is mainly eliminated by metabolism via thymidine phosphorylase (TPase) to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). Because TPase is found in the liver and gastrointestinal tract, patients with hepatic impairment may have higher FTD exposures than patients with normal hepatic function, which may lead to more treatment limiting severe toxicity.	<p>Complete a pharmacokinetic study to determine the appropriate dose of Lonsurf in patients with hepatic impairment.</p> <p>Final Protocol Submission: Submitted</p> <p>Trial Completion: 9/30/ 2017</p> <p>Final Report Submission: 12/31/2017</p>
Should the dose of Lonsurf be reduced in patients with severe renal impairment?	The pharmacokinetic modulator tipiracil (TPI) in Lonsurf is a thymidine phosphorylase (TPase) inhibitor, which is primarily eliminated by urinary excretion in its unchanged form. Patients with renal impairment may have increased TPI exposure leading to increasing in trifluridine (FTD) exposure due to increased inhibition of FTD metabolism (via TPase) by TPI, which may lead to more treatment limiting severe toxicity.	<p>Complete a pharmacokinetic study to determine the appropriate dose of Lonsurf in patients with renal impairment.</p> <p>Final Protocol Submission: Submitted</p> <p>Trial Completion: 9/30/ 2017</p> <p>Final Report Submission: 12/31/2017</p>

### 1.2.2 Post Marketing Commitments

None.

### 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

TAS-102 (Lonsurf) is a combination of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5 (weight ratio, 1:0.471) formulated in an immediate-release, film coated tablet with two strengths of 15 mg and 20 mg (expressed as mg of trifluridine per tablet).

**Mechanism of Action:** Trifluridine is an antineoplastic thymidine-based nucleoside analog, which can be incorporated into deoxyribonucleic acid (DNA) in tumor cells following phosphorylation and inhibit the tumor cell proliferation. Tipiracil is a thymidine phosphorylase (TPase) inhibitor and inhibits degradation of trifluridine by inhibiting TPase, thus increasing systemic exposure to trifluridine when tipiracil is given together with trifluridine.

**Clinical Dose Selection:** The proposed dosing regimen of Lonsurf is 35 mg/m<sup>2</sup>/dose administered orally twice daily (BID), within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, repeated in each 28-days cycle. The tolerability TAS-102 was evaluated at dose levels of 15, 20, 25, 30, and 35 mg/m<sup>2</sup> in a Phase 1 dose-finding study conducted in Japanese patients with advanced solid tumors (Study J001-10040010). The tolerability and safety at dose levels of 30 and 35 mg/m<sup>2</sup> were further confirmed in Western (US) patients with mCRC (Study TPU-TAS-102-101). The efficacy and safety of TAS-102 at 70 mg/m<sup>2</sup>/day (35 mg/m<sup>2</sup> BID) as the proposed dosage regimen were established in the registration Study TPU-TAS-102-301 (RECOURSE) and supported by a Phase 2 study in Japanese patients with mCRC (Study J003-10040030).

**Exposure/Dose-Response Relationship for Efficacy and Safety:** The E-R relationship for efficacy and safety could not be adequately characterized as only 26% (138/534) patients in the TAS-102 treatment arm of the registration trial Study RECOURSE (TPU-TAS-102-301) had evaluable PK data. The median overall survival (OS) rate appeared more favorable in the subpopulation with higher trifluridine AUCs compared to the subpopulation with lower trifluridine AUCs (9.2 vs. 8.1 months). The incidence of Grade  $\geq 3$  neutropenia and any Grade  $\geq 3$  drug related AEs appear higher (>10%) in the group with higher trifluridine AUC compared with the group with lower trifluridine AUC. The rate of any dose reduction was also higher in the group with higher trifluridine AUC group (23%) compared with the group with lower trifluridine AUC group (9%).

**Pharmacokinetics:** Systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 to 35 mg/m<sup>2</sup>. The mean elimination half-life ( $t_{1/2}$ ) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose of 35 mg/m<sup>2</sup> Lonsurf. The mean elimination  $t_{1/2}$  at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours. The accumulation of trifluridine was 3-fold for AUC<sub>0-last</sub> and 2-fold for peak plasma concentration ( $C_{max}$ ) at steady-state while no accumulation was observed for tipiracil. Administration of a single dose of TAS-102 containing tipiracil and trifluridine 35 mg/m<sup>2</sup> increased the mean AUC<sub>0-last</sub> of trifluridine by 37-fold and  $C_{max}$  by 22-fold with reduced variability compared to trifluridine 35 mg/m<sup>2</sup> alone.

**Food Effect:** A standardized high-fat, high-calorie meal decreased trifluridine  $C_{max}$ , tipiracil  $C_{max}$  and AUC by 40-45%, but did not change trifluridine AUC compared to the fasting condition in

patients with cancer following administration of a single dose of Lonsurf 35 mg/m<sup>2</sup>. It is recommended to take Lonsurf within 1 hour after completion of the morning and evening meals based on the observed correlation between the increase in the C<sub>max</sub> of trifluridine and the decrease in neutrophil counts.

**ADME:** The mean relative bioavailability of TAS-102 tablets compared to oral solution is 100% for trifluridine and 96% for tipiracil. Trifluridine mainly binds to human serum albumin. The *in vitro* protein binding in human plasma is greater than 96 % for trifluridine and below 8% for tipiracil. Trifluridine and tipiracil were not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine was mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, FTY, with 5-carboxyuracil (5-CU) and 5-carboxy-2'-deoxyuridine (5-CdUrd) as minor components. Following a single 60 mg TAS-102 administration (Study TPU-TAS-102-104), the mean 48 hours cumulative urinary excretion was 1.5 % for unchanged trifluridine, 19.2 % for FTY and 29.3% for unchanged tipiracil. The major elimination pathway of trifluridine is metabolism by TPase and the major metabolite FTY is excreted into the urine, while tipiracil was mainly excreted in unchanged form in the urine.

**Population Pharmacokinetic Analysis:** Population PK analyses with data from 239 patients who received TAS-102 treatment indicated that body size and renal function are the primary intrinsic factors affecting the exposure to trifluridine and to tipiracil after TAS-102 administration. Oral clearance of trifluridine also negatively correlated with serum albumin probably due to the high protein binding of trifluridine. Other covariates tested including age, sex, race, mild hepatic impairment, and concomitant administration of OCT2 inhibitor had no clinically meaningful impact on exposure to trifluridine or tipiracil. The proposed body surface area (BSA) adjusted dosing is justified.

**Renal Impairment:** In Study RECURSE, the mean values of AUC for trifluridine at steady state were 31% higher in patients with mild (CL<sub>cr</sub> = 60-89 mL/min, n=38) and 43% higher in patients with moderate (CL<sub>cr</sub> = 30 to 59 mL/min, n= 16) renal impairment than those in patients with normal (CL<sub>cr</sub> ≥ 90 mL/min, n=84) renal function. Similar effect of renal impairment on the tipiracil exposure was observed (34% higher in patients with mild and 68% higher in patients with moderate renal impairment than that in patients with normal renal function). The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment (CL<sub>cr</sub> < 30 mL/min) or end-stage renal disease. The increased exposures of trifluridine and tipiracil in patients with mild to moderate impairment might be confounded by the relatively smaller body weights in the mild (median body weight=64 kg, n= 38) and moderate (median body weight=59 kg, n=16) renal impaired patients when compared to normal renal function (median body weight=78 kg, n=84). Since tipiracil is a PK modulator increasing the systemic exposure of trifluridine by inhibiting TPase, the increased exposure of trifluridine in patients with mild to moderate renal impairment could be the secondary effect mediated by the increased tipiracil exposures leading to increased inhibition of trifluridine metabolism (via TPase) in the same patients with renal impairment. A dedicated renal impairment is currently on going and will be submitted as a PMR study.

***Hepatic Impairment:*** Mild hepatic impairment had no clinically meaningful effect on exposure of either trifluridine or tipiracil as compared to patients with normal liver function. Patients with moderate ( $1.5 \times \text{ULN} \leq \text{TB} < 3 \times \text{ULN}$  and any AST) or severe ( $\text{TB} \geq 3 \times \text{ULN}$  and any AST) hepatic impairment were not enrolled in Study RECURSE. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with moderate to severe hepatic impairment. The exposure of trifluridine in patients with mild hepatic impairment might be confounded by the body weight and/or different liver TPase level in the patients with mild impaired hepatic function (median body weigh=66 kg, n= 42) when compared to the patients with normal hepatic function (median body weigh=72 kg, n= 96). A dedicated hepatic impairment is currently on going and will be reported as a PMR study.

**Signatures:**

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Xianhua (Walt) Cao, Ph.D.  
Reviewer  
Division of Clinical Pharmacology V

---

Hong Zhao, Ph.D.  
Team Leader  
Division of Clinical Pharmacology V

---

Jingyu (Jerry) Yu, Ph.D.  
Reviewer  
Division of Pharmacometrics

---

Yaning Wang, Ph.D.  
Division Deputy Director  
Division of Pharmacometrics

---

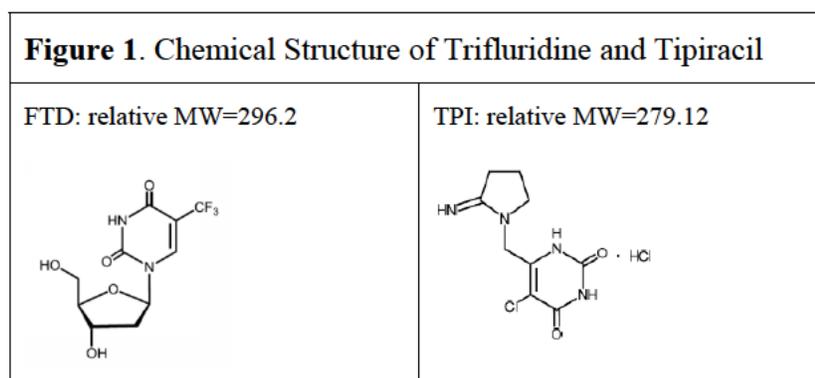
NAM Atiqur Rahman, Ph.D.  
Division Director  
Division of Clinical Pharmacology V

## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

**2.1.1** *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

TAS-102 (Lonsurf) is a combination product of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio 1:0.5 (weight ratio, 1:0.471). The molecular weight is 296.2 g/mol for trifluridine and 279.1 g/mol for tipiracil. Chemical structures of trifluridine and tipiracil are shown in [Figure 1](#).



The pharmacologically active components of TAS-102 (FTD and TPI) are formulated in an immediate-release, film coated tablet form, with two strengths of 15 mg and 20 mg (expressed as mg of trifluridine).

Trifluridine and tipiracil exhibited low membrane permeability across Caco-2 cell monolayers and high solubility in buffer solutions ranging in pH values from 1 to 7.5 ([Table 1](#)). Both trifluridine and tipiracil are considered as Biopharmaceutics Classification System (BCS) III compounds.

**Table 1.** Trifluridine and Tipiracil Drug Substance Solubility Profile:

Characteristic	Results	
	FTD	TPI
Highest dose administered:	80 mg	37.68 mg
Solubility:	(b) (4) (pH 1 – 7.5)	(b) (4) (pH 1 – 7.5)
Dose solubility:	1.3 mL (i.e. < 250 mL)	0.31 mL (i.e. < 250 mL)
BCS Class:	(b) (4)	

BCS = Biopharmaceutics Classification System; FTD = trifluridine; TPI = tipiracil

<sup>1</sup> A drug substance is considered highly soluble when the highest dose strength is soluble in < 250 mL of water over a pH range of 1 to 7.5

(b) (4)

Source: Summary of Biopharmaceutics Studies, Table 3, Page 11.

### 2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Trifluridine is an antineoplastic thymidine-based nucleoside analog, which can be incorporated into deoxyribonucleic acid (DNA) in tumor cells following phosphorylation and inhibit the tumor cell proliferation. Tipiracil inhibits degradation of trifluridine by inhibiting thymidine phosphorylase (TPase), thus increasing systemic exposure to trifluridine when tipiracil is given together with trifluridine.

The proposed indication is for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

### 2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regimen of Lonsurf is 35 mg/m<sup>2</sup>/dose (based on trifluridine) administered orally twice daily (BID), within 1 hour after completion of morning and evening meals, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

#### Clinical Pharmacology Studies

The clinical pharmacology program included seven clinical trials as described in Table 2. The PK profiles of trifluridine and tipiracil after dosing of TAS-102 were characterized using non-compartment analysis (NCA) and population PK (PopPK) analyses based on data collected from 239 patients administered with the proposed dose regimen in Studies J001-10040010, TPU-TAS-102-102, TPU-TAS-102-103, and TPU-TAS-102-301 (RECOURSE). Exploratory exposure-response (E-R) analyses were conducted with the evaluable PK data collected from 138 Lonsurf-treated patients in the registrational study RECOURSE.

<b>Study No.</b>	<b>Population</b>	<b>Assessment</b>	<b>Dosage and Regimen<sup>a</sup></b>	<b>N<sup>b</sup></b>
J001-10040010	Japanese patients with confirmed solid tumors	Dose finding	15, 20, 25, 30, and 35 mg/m <sup>2</sup> under proposed dosage regimen	21
J004-10040040	Japanese patients with solid tumors	Food Effect	2 single doses of 35 mg/m <sup>2</sup> with ≥5 days washout, followed with extension	16
TPU-TAS-102-101	US Patients with refractory mCRC	Dose finding to determine the RP3D	30 or 35 mg/m <sup>2</sup> under proposed dosage regimen	27 <sup>c</sup>

TPU-TAS-102-102	US Patients with advanced solid tumors	PK contribution of TPI	Single dose of 35 mg/m <sup>2</sup> TAS-102 or FTD at cycle 1 day 1, then followed with extension	39
TPU-TAS-102-103	US patients with advanced solid tumors	Cardiac Safety	35 mg/m <sup>2</sup> under proposed dosage regimen	41
TPU-TAS-102-104	US patients with advanced solid tumors	Relative bioavailability	60 mg PO (tablet [3×20 mg] or solution, 3 single doses with 7- day washout, followed with extension	38
TPU-TAS-102-301 (RECOURSE)	Global patients with mCRC who had received ≥2 prior regimens of standard chemotherapies	Major efficacy and safety study	35 mg/m <sup>2</sup> under proposed dosage regimen	138

**Notes:** a, Regimen: BID x 5 days a week followed by 2 days rest for 2 weeks every 4 weeks.

b, Subject number with PK data evaluable;

c, PK were not evaluated; RP3D: recommended phase 3 dose

## Clinical Studies

### Metastatic colorectal cancer (mCRC)

The proposed indication in the current NDA is primarily supported by the results from Study TPU-TAS-102-301 (n=534 TAS-102-treated) (Table 3).

<b>Table 3.</b> Description of the Major Clinical Study:		
<b>Study No.</b>	<b>Study Design</b>	<b>Results of Endpoints<sup>1</sup></b>
TPU-TAS-102-301 (RECOURSE)	Phase 3, placebo-controlled, multicenter, double-blinded, randomized study of TAS-102 + BSC versus placebo + BSC in patients with mCRC who had received ≥2 prior regimens of standard chemotherapies and were refractory to or failing those Chemotherapies.  Totally 800 patients were randomized with 534 patients in TAS-102 treated arm.	Primary: overall survival (OS) Median OS: 7.1 months for the TAS-102 arm versus 5.3 months for the placebo arm)  Secondary: progression-free survival (PFS), safety and tolerability. Median PFS: 2.0 months for the TAS-102 arm versus 1.7 months for the placebo arm.

<sup>1</sup>As reported by Taiho;

Using a treatment allocation of 2:1 (TAS-102: placebo) of 800 patients, a target of 571 events (deaths) was required for the primary analysis. At the time of analysis, events were observed for 364 (68.2%) patients in the TAS-102 arm and 210 (78.9%) patients in the placebo arm. The overall median follow-up for all patients was 11.8 months.

The addition of TAS-102 to BSC resulted in a clinically meaningful and statistically significant improvement in OS compared to placebo plus BSC with a hazard ratio (HR) of 0.68 (95% CI: 0.58, 0.81), and 1- and 2-sided  $p < 0.0001$  (stratified log-rank test). The median OS was 7.1 months for the TAS-102 arm versus 5.3 months for the placebo arm (Table 4).

**Table 4.** Overall Survival (ITT Population) in Study RECURSE

	<b>Lonsurf (N=534)</b>	<b>Placebo (N=266)</b>
<b>Overall Survival</b>		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months) <sup>a</sup> (95% CI) <sup>b</sup>	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
Hazard ratio [95% CI]	0.68 (0.58, 0.81)	
P-value <sup>c</sup>	<0.001	
<b>Progression-Free Survival</b>		
Number of Progression or Death, N (%)	472 (88)	251 (94)
Median PFS (months) <sup>a</sup> (95% CI) <sup>b</sup>	2.0 (1.9, 2.1)	1.7 (1.7, 1.8)
Hazard ratio (95% CI)	0.48 (0.40, 0.55)	
P-value	<0.001	
<b>Overall Response Rate</b>		
ORR (Complete or partial), N (%) [95% CI] <sup>e</sup>	8/502 (1.6) [0.7, 3.1]	1/258 (0.4) [0.0, 2.1]

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

<sup>c</sup> Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region)

Source: FDA Labeling Review, Table 3.

### **2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?**

The primary efficacy outcome measure of the registration trial RECURSE was OS. The study was designed to detect with 90% power an OS hazard ratio (HR) of 0.75 (25% risk reduction) for TAS-102 compared to placebo with a 1-sided type I error of 0.025. The key secondary endpoints were PFS, safety and tolerability. Additional outcome measures included time to treatment failure (TTF), overall response rate (ORR), disease control rate (DCR), duration of response (DR) and time to Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or higher.

### **2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?**

Yes. The components of TAS-102, trifluridine and tipiracil, along with their metabolites including the major inactive metabolite, 5-(trifluoromethyl) uracil (FTY), were appropriately identified and measured in plasma and urine to assess PK parameters after oral administration.

## 2.2.4 Exposure-response

### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The E-R relationship for efficacy could not be adequately characterized due to data limitation. Exploratory exposure-response (E-R) analyses were conducted with the evaluable PK data collected from 138/534 (26%) TAS-102 treated patients (PK/PD population) in the registrational study RECOURSE. The relationships for OS between the TAS-102 arm and the placebo arm, and the TAS-102 PK/PD population are shown in Table 5 and displayed graphically in Figure 2. The HR of OS and associated medians for the trifluridine and tipiracil high/low AUC subpopulation are presented in Table 6. For trifluridine, median OS appeared more favorable in the subpopulation with higher trifluridine AUCs compared to the subpopulation with lower trifluridine AUCs (9.2 vs. 8.1 months). For tipiracil, the trend of the OS effect was not as pronounced, but was in favor of the lower tipiracil AUC subpopulation compared to the subpopulation with high AUCs (9.2 vs. 7.8 months). Refer to the Pharmacometrics Review.

**Table 5.** Overall Survival in the TAS-102 Arm ,the TAS-102 PK/PD Population, and the Placebo Arm

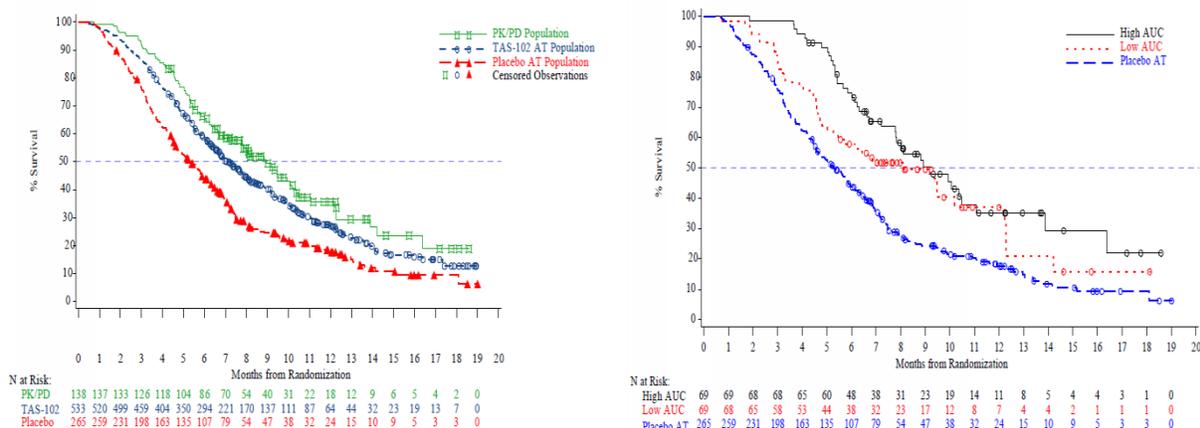
Parameter	TAS-102 (N=533)	TAS-102 PK/PD Population (N=138)	Placebo (N=265)
<b>Number (%) of patients by censoring status</b>			
Total	533 (100.0)	138 (100.0)	265 (100.0)
Not censored (dead)	363 (68.2)	81 (58.7)	209 (78.9)
Censored	170 (31.8)	57 (41.3)	56 (21.1)
<b>Median Survival (months)<sup>a</sup>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

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

Source: sponsor's PK/PD study report for Study TPU-TAS-102-301 Table 6 page 15

**Figure 2.** Survival in the PK/PD Population and by Trifluridine AUC



Source: Source: sponsor's PK/PD study report for Study TPU-TAS-102-301 Figure 1 and Figure 2

**Table 6. Overall Survival by Trifluridine AUC and by Tipiracil AUC (PK/PD Population)**

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

<sup>a</sup> Kaplan-Meier estimates

<sup>b</sup> Methodology of Brookmeyer and Crowley

Source: sponsor's PK/PD study report for Study TPU-TAS-102-301 Table 7 page 17

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

The E-R relationship for safety could not be adequately characterized as only 26% percent (138/534) patients in the TAS-102 treatment arm in the registrational study RECURSE had evaluable PK data. Grade 3 or higher adverse events (AEs) for trifluridine or tipiracil AUC in the PK/PD population are summarized in Table 7. The incidence of Grade  $\geq 3$  neutropenia and any Grade  $\geq 3$  drug related AEs were higher ( $>10\%$ ) in the trifluridine high AUC group compared with the low AUC group. The rate of any dose reduction was higher in the trifluridine high AUC group (23%) compared with the low AUC group (9%). No specific pattern emerged between the tipiracil high AUC group and the low AUC group. Refer to the Pharmacometrics Review.

**Table 7. Safety Event Summary by Trifluridine or Tipiracil AUC (PK/PD Population)**

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

<sup>a</sup> Grade 3 or higher based on laboratory data.

<sup>b</sup> Dose reductions based on exposure data.

n=number of patients with an event.

Source: sponsor's PK/PD study report for Study TPU-TAS-102-301 Table 10 page 23

### 2.2.4.3 Does this drug prolong the QT/QTc interval?

TAS-102 administered to 42 patients with advanced solid tumors at the recommended dosage regimen had no large effect (i.e.,  $> 20$  ms) in the mean QTc interval when compared to placebo and no evident exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc

greater than 500 msec during TAS-102 treatment and 1 of 42 patients (2.4%) had a QTc increase from baseline greater than 60 msec. Refer to FDA QT-IRT review.

**2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?***

Phase 1 dose-finding study conducted in Japanese patients with advanced solid tumors showed that TAS-102 was tolerated in doses up to 70 mg/m<sup>2</sup>/day (35 mg/m<sup>2</sup> BID) administered for 5 consecutive days a week with 2 days rest for 2 weeks, repeated every 4 week (Study J001-10040010). The tolerability of this dosage regimen was further confirmed in a Phase 1 dose-finding study conducted in Western (US) patients with mCRC (Study TPU-TAS-102-101). The efficacy and safety of TAS-102 with this dosage regimen was studied in a Japanese Phase 2 study in patients with mCRC (Study J003-10040030). Based on these data, this dosage regimen for TAS-102 was selected for the global registrational study RECOURSE. *What are the PK characteristics of the drug?*

**2.2.4.5 *What are the single dose and multiple dose PK parameters?***

PK contribution of tipiracil

PK contribution of tipiracil was conducted in Study TPU-TAS-102-102. Patients were randomized to receive a single oral dose of TAS-102 (35 mg/m<sup>2</sup>) (Group 1, n=19) or a single oral dose of trifluridine alone (35 mg/m<sup>2</sup>) (Group 2, n=20) in the morning of Day 1 of Cycle 1 (PK contribution part). Serials blood samples were collected within 12-hours post dosing for the single-dose PK analysis. Administration of a single dose of TAS-102 containing tipiracil and trifluridine 35 mg/m<sup>2</sup> (Group 1) increased the mean AUC<sub>0-last</sub> of trifluridine by 38-fold and C<sub>max</sub> by 22-fold with reduced variability compared to trifluridine 35 mg/m<sup>2</sup> alone (Table 8 and Figure 3). The mean C<sub>max</sub> for trifluridine after administration of trifluridine alone was 138 ng/mL (CV=92%, range: 25-504 ng/mL), while the mean C<sub>max</sub> for trifluridine after administration of TAS-102 was 2381 ng/mL (CV=44%, range: 979-4190 ng/mL).

Single dose and multiple doses PK

Plasma PK parameters for TAS-102 components (FTD and tipiracil) and the primary trifluridine metabolite FTY, following single- and multiple-dose administration of TAS-102 at 35 mg/m<sup>2</sup> BID under fed conditions (within 1 hour after completion of meals) across studies in patients with solid tumors are presented in Table 9 and Table 10. The PK parameters were consistent across the studies. In study TPU-TAS-102-102, plasma PK parameters following a single dose (Day 1 of Cycle 1) and following repeat dosing (Day 12 of Cycles 1, 2, and 3) were evaluated.

The mean elimination half-life (t<sub>1/2</sub>) of trifluridine was 1.4 hours after a single dose and 2.1 hours at steady state after 35 mg/m<sup>2</sup> TAS-102 BID administration. The mean elimination t<sub>1/2</sub> of tipiracil was 2.1 hours after a single dose and 2.4 hours at steady state. The accumulation of trifluridine was 3-fold for AUC<sub>0-last</sub> and 2-fold for C<sub>max</sub> at steady-state after BID dosing. No accumulation was observed for tipiracil.

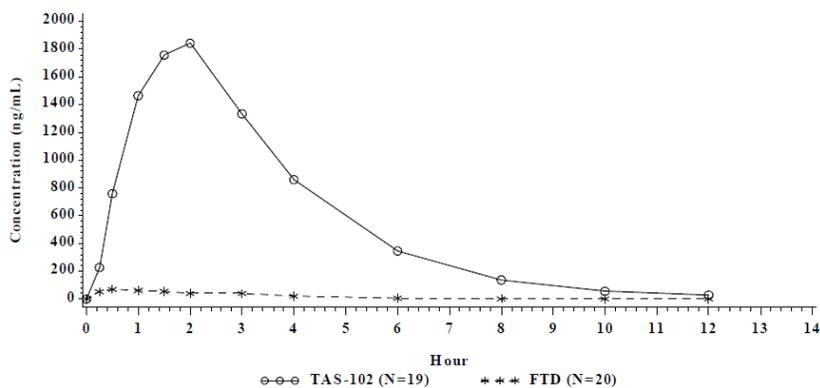
**Table 8.** Summary of AUC and C<sub>max</sub> of Trifluridine and FTY after a Single Dose of TAS-102 or Trifluridine alone at 35 mg/m<sup>2</sup>

Analyte Parameter	TAS-102		FTD		Ratio of Geometric Mean (TAS-102/FTD)	
	N	Geometric Mean	N	Geometric Mean	Estimate	(95% CI)
<b>FTD</b>						
AUC <sub>0-last</sub> (ng*hr/mL)	19	6618.07	20	176.27	37.545	(27.56 - 51.15)
C <sub>max</sub> (ng/mL)	19	2155.17	20	96.24	22.393	(14.19 - 35.34)
AUC <sub>0-inf</sub> (ng*hr/mL)	19	6693.97	10 <sup>a</sup>	247.88	27.004	(19.56 - 37.27)
<b>FTY</b>						
AUC <sub>0-last</sub> (ng*hr/mL)	19	3231.72	20	4121.90	0.784	(0.65 - 0.94)
C <sub>max</sub> (ng/mL)	19	736.75	20	1104.29	0.667	(0.54 - 0.82)
AUC <sub>0-inf</sub> (ng*hr/mL)	19	3320.23	20	4179.31	0.794	(0.66 - 0.96)

<sup>a</sup> Due to low and fluctuating plasma FTD concentrations after administration of FTD alone, AUC<sub>0-inf</sub> could only be determined for 10 patients.

Source: Summary of Clinical Pharmacology, Table 5, page 30

**Figure 3.** Mean Trifluridine Plasma Concentrations Time Profile after Single Dose of TAS-102 or Trifluridine alone (Study TPU-TAS-102-102)



Source: Summary of Clinical Pharmacology, Figure 6, page 29

**Table 9.** Single Dose TAS-102 PK Parameters across Studies- Mean ± SD (%CV)

Study	J001-10040010	J004-10040040		TPU-TAS-102-102	TPU-TAS-102-103	TPU-TAS-102-104
Dose, Fast/Fed	35 mg/m <sup>2</sup> , Fed	35 mg/m <sup>2</sup> , Fed	35 mg/m <sup>2</sup> , Fasted	35 mg/m <sup>2</sup> , Fed	35 mg/m <sup>2</sup> , Fed	60-mg fixed dose, Fasted <sup>a</sup>
Number of Patients	N=6	N=14	N=14	N=19	N=44	N=21
<b>FTD</b>						
C <sub>max</sub> (ng/mL)	3338 ± 767 (23)	3510±1380 (39.2)	5630±1840 (32.7)	2381.21±1047.61 (43.99)	2865.23±1275.13 (44.50)	4408.10±2228.51 (50.55)
T <sub>max</sub> (hr) <sup>b</sup>	1.3 (1.0, 2.0) (39)	1.32 (0.50, 4.00)	0.88 (0.25, 2.00)	1.99 (0.53, 4.00) (55.10)	2.08 (0.33, 6.08)(63.23)	1.23(0.25, 5.95) (98.30)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>c</sup>	8678 ± 1786 (21)	9840±4247 (43.2)	10648±5011 (47.1)	7044.53±2411.25 (34.23)	7948.47±2571.63 (32.35)	7105.03±3333.50 (46.92)
AUC <sub>0-inf</sub> (ng*hr/mL)	8672 ± 1710 (20)	10082±4593 (45.6)	10943±5581 (51.0)	7119.92±2412.10 (33.88)	8019.10±2607.59 (32.52)	7188.46±3452.97 (48.03)
T <sub>1/2</sub> (hr)	1.41 ± 0.38 (27)	1.72±0.58 (33.5)	2.13±0.76 (35.6)	1.42±0.42 (29.52)	1.47±0.31 (21.08)	1.77±0.47 (26.71)
<b>TPI</b>						
C <sub>max</sub> (ng/mL)	76.6±32.1 (42)	76.8±26.3 (34.3)	135±39 (29.0)	68.68 ±29.71 (43.25)	83.20±34.19 (41.09)	135.66±100.56 (74.12)
T <sub>max</sub> (hr) <sup>b</sup>	2.3±0.8 (35)	2.79 (1.00, 6.00)	2.07 (1.00, 4.00)	3.49±1.67 (47.93)	3.46 (1.08, 6.25) (44.49)	2.36±1.64 (69.22)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>c</sup>	281±99 (35)	361±160 (44.4)	647±281 (43.4)	300.54±126.92 (42.23)	371.84±158.76 (42.70)	536.06±264.41 (49.32)
AUC <sub>0-inf</sub> (ng*hr/mL)	302±96 (32)	384±189 (49.2)	677±309 (45.7)	330.57±143.01 (43.26), n=16	391.98±179.16 (45.71)	582.03±257.29 (44.21)
T <sub>1/2</sub> (hr)	1.67±0.22 (13)	2.22±0.45	2.19±0.66	2.10±0.47 (22.49), n=16	2.01±0.54 (27.08)	2.12±0.50 (23.67), n=20
<b>FTY</b>						
C <sub>max</sub> (ng/mL)	878±228 (26)	728±186 (25.6)	860±207 (24.1)	764.89±201.44 (26.34)	904.05±286.95 (31.74)	1093.38±339.55 (31.05)
T <sub>max</sub> (hr) <sup>b</sup>	2.0 (2.0, 2.0)	1.96 (0.50, 4.00)	1.43 (1.00, 2.00)	2.69 (1.00, 6.08) (46.30)	2.68 (0.58, 6.25) (54.42)	1.57 (0.47, 5.95) (73.06)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>c</sup>	3165±341 (11)	3011±855 (28.4)	2900±837 (28.9)	3343.75±897.48 (26.84)	3735.91±1067.64 (28.58)	3643.60±1109.78 (30.46)
AUC <sub>0-inf</sub> (ng*hr/mL)	3492±693 (20)	3121±941 (30.2)	2972±868 (29.2)	3435.59±924.88 (26.92)	3809.38±1112.64 (29.21)	3716.41±1120.40 (30.15)
T <sub>1/2</sub> (hr)	1.57±0.38 (24)	2.08±0.69	2.41±0.61	1.76±0.38 (21.49)	1.62±0.24 (14.81)	1.66±0.46 (27.54)

<sup>a</sup> This dose approximates a single 35 mg/m<sup>2</sup> dose for an individual with normal body weight.

<sup>b</sup> Median (min, max) is presented for T<sub>max</sub>.

<sup>c</sup> AUC<sub>0-12</sub> for Study J004-10040040 and AUC<sub>0-last</sub> for Studies TPU-TAS-102-102, TPU-TAS-102-103 and TPU-TAS-102-104.

Notes: Minor metabolites are not included.

Source: Adapted from Table 20, Summary of Clinical Pharmacology Studies

**Table 10.** Multiple Dose TAS-102 PK Parameters across Studies- Mean ± SD (%CV)

Study	J001-10040010	TPU-TAS-102-102	TPU-TAS-102-103
Cycle/Day Dose Fast/Fed	Cycle 1 Day 12 35 mg/m <sup>2</sup> BID on Days 1-5 and 8-12 Fed	Cycle 1 Day 12 35 mg/m <sup>2</sup> BID on Days 1-5 and 8-12 Fed	Cycle 1 Day 12 35 mg/m <sup>2</sup> BID on Days 1-5 and 8-12 Fed
Number of Patients	N=6	N=34	N=40
<b>FTD</b>			
C <sub>max</sub> (ng/mL)	4752±1697 (36)	4857.06±1930.19 (39.74)	5447.75±2693.94 (49.45)
T <sub>max</sub> (hr) <sup>a</sup>	1.9±1.6 (85)	2.20 (0.50, 8.00) (84.60)	2.45 (0.33, 6.08) (62.32)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>b</sup>	20950±2237 (11)	23696.93±7419.01 (31.31)	24545.94±9059.35 (36.91)
AUC <sub>0-inf</sub> (ng*hr/mL)	20950±2237 (11)	--	25973.32±10126.96 (38.99)
T <sub>1/2</sub> (hr) <sup>c</sup>	1.97±0.51 (26)	2.07±0.43 (20.64), n=26	2.20±0.72 (32.70)
<b>TPI</b>			
C <sub>max</sub> (ng/mL)	70.0±43.4 (62)	69.35±27.45 (39.58)	78.51±28.07 (35.75)
T <sub>max</sub> (hr) <sup>a</sup>	2.3 ±0.8 (35)	3.15 (1.00, 8.03)	3.00 (1.08, 6.08) (47.27)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>b</sup>	317±182 (57)	372.13±134.71 (36.20)	382.58±120.79 (31.57)
AUC <sub>0-inf</sub> (ng*hr/mL)	317±182 (57)	--	410.38±136.20 (33.19), n=39
T <sub>1/2</sub> (hr) <sup>c</sup>	2.37±0.93 (40)	2.40±0.59 (24.49), n=19	2.34±0.64 (27.21), n=39
<b>FTY</b>			
C <sub>max</sub> (ng/mL)	560±92 (16)	678.76±199.77 (29.43)	717.80±184.38 (25.69)
T <sub>max</sub> (hr) <sup>a</sup>	23±1.4 (59)	2.78 (0.50, 8.00)	2.77 (0.58, 6.08)
AUC <sub>0-10</sub> (ng*hr/mL) <sup>b</sup>	3622±1094 (30)	5206.27±2055.07 (39.47)	5163.60±1709.70 (33.11)
AUC <sub>0-inf</sub> (ng*hr/mL)	3622±1094 (30)	--	4902.57±1254.24 (25.58), n=16
T <sub>1/2</sub> (hr) <sup>c</sup>	7.27±2.95 (41)	4.51±0.53 (11.74), n=9	4.12±0.81(19.66), n=16

-- = not determined

<sup>a</sup> Median (min, max) is presented for T<sub>max</sub>.

<sup>b</sup> AUC<sub>0-last</sub> is presented for Studies TPU-TAS-102-102 and TPU-TAS-102-103.

<sup>c</sup> CV not calculated for t<sub>1/2</sub>.

Notes: Minor metabolites are not included.

Source: Adapted from Table 21, Summary of Clinical Pharmacology Studies

#### **2.2.4.6 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

No studied with TAS-102 has been conducted in healthy volunteer.

#### **2.2.4.7 What are the characteristics of drug absorption?**

Following a single oral administration of TAS-102 at 35 mg/m<sup>2</sup> within 1 hour after completion of meals in patients with cancer, the mean time to peak plasma concentration (T<sub>max</sub>) was around 2 hours for trifluridine and 3.5 hours for tipiracil after dosing (Table 9).

The mean relative bioavailability of TAS-102 tablets compared to oral solution is 100% (90% CI: 0.93-1.09) for trifluridine and 96% (90% CI: 0.86-1.07) for tipiracil (See Table 24 under section 2.5.2).

A standardized high-fat, high-calorie meal decreased trifluridine C<sub>max</sub>, tipiracil C<sub>max</sub> and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in cancer patients taking single dose of 35 mg/m<sup>2</sup> TAS-102 ( See Table 25 under section 2.5.3). Since trifluridine C<sub>max</sub> is correlated with neutropenia (see Figure 6 under section 2.2.4.12), taking TAS-102 with food is recommended.

#### **2.2.4.8 What are the characteristics of drug distribution?**

Trifluridine mainly binds to human serum albumin. The *in vitro* protein binding of trifluridine in human plasma is greater than 96%, independent of drug concentration range of 0.5 to 50 µg/mL and presence of tipiracil (5 µg/mL) [Study AE-2350-3G]. Plasma protein binding of tipiracil is below 8% [Study AE-2350-2G]. The mean human blood to plasma ratio was approximately 0.6 over the concentration range of 0.5 to 50 µg/mL for trifluridine and 0.01 to 1 µg/mL for tipiracil [Study 11DA34].

The apparent volume of distribution values (Vd/F) were 21 L (CV=46%) for trifluridine and 333 L (CV=53%) for tipiracil after a single oral dose of 35 mg/m<sup>2</sup> TAS-102 tablets under fed conditions in cancer patients (Study TPU-TAS-102-102). The population PK analyses estimated mean Vd/F values were 10 L for trifluridine (CV=25%) and 192 L for tipiracil (CV=63%) in cancer patients (Study 12DA25).

#### **2.2.4.9 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

No mass balance study for TAS-102 has been conducted.

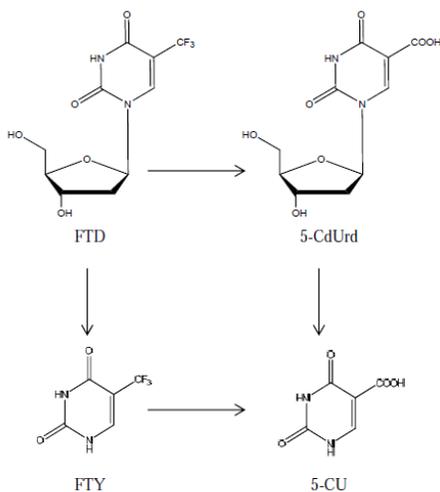
#### **2.2.4.10 What are the characteristics of drug metabolism?**

Trifluridine and tipiracil were not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine was mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, FTY, with 5-carboxyuracil (5-CU) and 5-carboxy-2'-deoxyuridine (5-

CdUrd) as minor components. Following oral administration of TAS-102 at the doses of 30 to 70 mg/m<sup>2</sup>/day, concentrations of 6-hydroxymethyluracil (6-HMU) were only quantifiable in plasma at higher doses of TAS-102 (50 to 70 mg/m<sup>2</sup>/day). Concentrations of 6-HMU were approximately 1 to 2 ng/mL in plasma and were below the limit of quantification (50 ng/mL) in urine. No other metabolites were detected in plasma or urine in clinical studies.

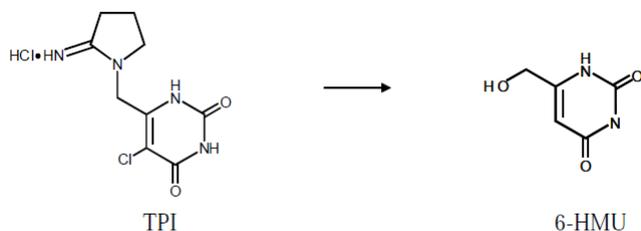
The proposed metabolic pathways for trifluridine and tipiracil in humans are shown in [Figure 4](#) and [Figure 5](#).

**Figure 4.** Proposed Metabolic Pathways of Trifluridine in Humans



**Source:** Summary of Clinical Pharmacology, Figure 2, Page 17

**Figure 5.** Proposed Metabolic Pathways of Tipiracil in Humans



**Source:** Summary of Clinical Pharmacology, Figure 3, Page 18

#### 2.2.4.11 What are the characteristics of drug excretion?

Following a single 60 mg TAS-102 administration (Study TPU-TAS-102-104), the mean 48 hours cumulative urinary excretion was 1.5 % for unchanged trifluridine, 19.2 % for FTY and 29.3% for unchanged tipiracil ([Table 11](#)).

The major elimination pathway of trifluridine is metabolism by TPase and the major metabolite FTY is excreted into the urine, while tipiracil was mainly excreted in unchanged form in the

urine.

Since tipiracil is a pharmacokinetic modulator that enhances the systemic exposure of trifluridine by inhibiting TPase, the clearance of trifluridine would be influenced by tipiracil plasma concentration. Thus, the increased exposure of trifluridine in mild and moderate renal impairment patients could be the secondary effect mediated by the increased tipiracil exposures leading to increased inhibition of trifluridine metabolism (via TPase) in the renal impairment patients. Refer to [section 2.3.1.5](#)

**Table 11.** Urinary Excretion of TAS-102 Components and Trifluridine Metabolites after Administration of TAS-102 Tablet

Analyte	Percentage of Administered Parent Dose Excreted <sup>a</sup> (%)		
	N	Mean	SD
FTD (unchanged)	36	1.5	1.50
FTY	36	19.2	8.28
5-CdUrd	36	0.0	0.00
5-CU	36	0.3	0.39
<b>Total<sup>b</sup></b>		21.0	9.07
TPI (unchanged)	36	29.3	17.03

<sup>a</sup> Based on molar equivalents.

<sup>b</sup> Sum of unchanged FTD and its metabolites.

Source: CSR Study TPU-TAS-102-104 Table 16, Page 66

#### **2.2.4.12 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?**

In Study J001-10040010, five escalating dose levels of 15, 20, 25, 30, and 35 mg/m<sup>2</sup> TAS-102 BID were evaluated in Japanese patients with solid tumors. Serial blood samples were collected for PK evaluation on Day 1 and Day 12. The AUC<sub>0-10h</sub> of trifluridine increased more than dose-proportionally over the dose range of 15 to 35 mg/m<sup>2</sup>. The dose-normalized AUC<sub>0-10h</sub> for trifluridine at the dose range of 40 to 70 mg/m<sup>2</sup>/day was generally constant (with differences ≤ 30%). Other parameters of trifluridine and parameters of tipiracil appeared to be dose proportional ([Table 12](#) and [Table 13](#)).

**Table 12.** Pharmacokinetic Parameters (Mean±SD) of Trifluridine in the Plasma Following Single- and Multiple-dose Administration (Study J001-10040010)

Dose (mg/m <sup>2</sup> /dose)	Day	n	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>0-10</sub> (ng.hr/mL)	T <sub>1/2</sub> (hr)
<b>Single-dose administration</b>						
15	1	6	1009±491	1.7±1.3	2037±773	1.39±0.38 <sup>a</sup>
20	1	3	1840±737	1.2±0.8	4347±535	1.17±0.15
25	1	3	2450±1021	1.5±0.9	4281±1380	1.49±0.59
30	1	3	3677±1459	1.2±0.8	8229±1441	1.88±0.73
35	1	6	3338±767	1.3±0.5	8678±1786 <sup>a</sup>	1.41±0.38
<b>Multiple-dose administration</b>						
15	12	6	1205±421	1.6±0.7	5478±2849	2.44±1.57
20	12	3	2747±610	1.7±0.6	9994±2109	1.52±0.34
25	12	3	2757±1173	1.3±0.6	8656 <sup>b</sup>	1.96±0.10
30	12	3	5437±1685	1.3±0.6	23672±7844	2.33±1.26
35	12	6	4752±1697	1.9±1.6	20950±2237	1.97±0.51

<sup>a</sup> n=5  
<sup>b</sup> n=2

Source: Summary of Clinical Pharmacology Studies, Table 2, Page 23

**Table 13.** Pharmacokinetic Parameters (Mean±SD) of Tipiracil in the Plasma Following Single- and Multiple-dose Administration (Study J001-10040010)

Dose (mg/m <sup>2</sup> /dose)	Day	n	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC <sub>0-10</sub> (ng.hr/mL)	T <sub>1/2</sub> (hr)
<b>Single-dose administration</b>						
15	1	6	25.8±14.7	2.6±1.6	117±84	2.27±0.74
20	1	3	43.1±6.5	1.7±0.6	166±29	1.53±0.17
25	1	3	54.2±28.5	1.7±0.6	214±79	1.78±0.27
30	1	3	136±77	2.7±1.2	521±338	1.66±0.37
35	1	6	76.6±32.1	2.3±0.8	281±99 <sup>a</sup>	1.67±0.22
<b>Multiple-dose administration</b>						
15	12	6	44.1±51.8	2.8±1.5	234±283	2.89±0.83
20	12	3	41.8±14.7	2.7±1.2	161±41	1.82±0.18
25	12	3	50.2±13.1	2.7±1.2	300 <sup>b</sup>	4.01±3.57
30	12	3	99.6±43.8	2.7±1.2	447±278	2.21±0.62
35	12	6	70.0±43.4	2.3±0.8	317±182	2.37±0.93

<sup>a</sup> n=5  
<sup>b</sup> n=2

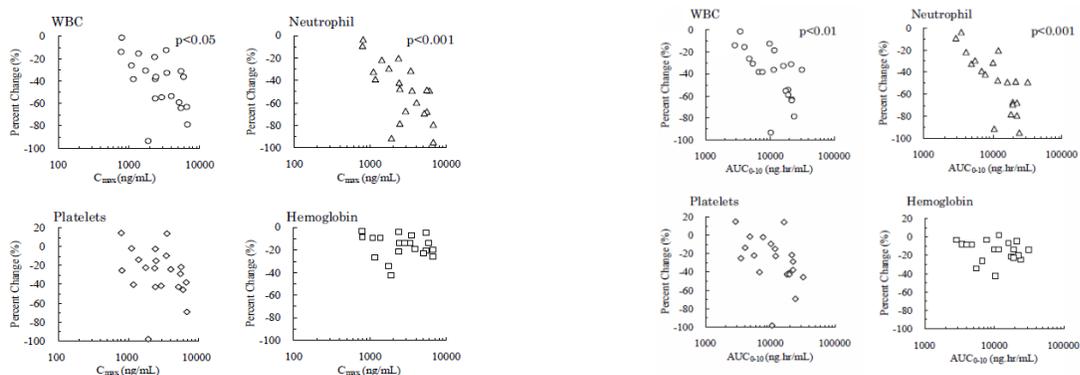
Source: Summary of Clinical Pharmacology Studies, Table 4, Page 24

The hematological parameters including the white blood cell (WBC), neutrophil, red blood cell (RBC), hemoglobin and platelet counts were evaluated throughout the study. The correlation between the rates of decrease in hematologic parameters and the C<sub>max</sub> and AUC<sub>0-10h</sub> of trifluridine post TAS-102 dosing is shown in Figure 6 below. In Cycle 1, the data on neutrophil count and white blood cell count were significantly correlated with the C<sub>max</sub> and AUC<sub>0-10h</sub> of trifluridine, FTY and tipiracil.

**Figure 6.** Correlation Between the Rates of Decrease in the Hematologic Parameters (%) and Trifluridine Exposure on Day 12 (Study J001-10040010)

FTD C<sub>max</sub>

FTD AUC<sub>0-10</sub>



Source: CSR Study J001-10040010, Figure 11.4.1.5-3 and 11.4.1.5-4

### 2.2.4.13 How do the PK parameters change with time following chronic dosing?

In study TPU-TAS-102-102, PK parameters were evaluated for TAS-102 components and the major metabolite FTY on Day 1 of Cycle 1 (single dose) and on Day 12 of Cycles 1, 2 and 3 after multiple dose administration of TAS-102 at 35 mg/m<sup>2</sup>. The accumulation of trifluridine was 3-fold for AUC<sub>0-last</sub> and 2-fold for C<sub>max</sub> at steady-state on Day 12 of Cycle 1 when compared to the parameters on Day 1 Cycle 1 (Table 14). There was no indication of further accumulation for trifluridine with successive cycles of TAS-102 administration (i.e., Day 12 of Cycle 2 and of Cycle 3 compared to that of Cycle 1). No accumulation was observed for tipiracil and FTY.

**Table 14.** Single- and Multiple-dose Pharmacokinetics of TAS-102 Components and Metabolite FTY (Study TPU-TAS-102-102)

Analyte Parameter	Single-dose PK (N=19)		Multiple-dose PK (At Least 1 Cycle) (N=38)					
	Cycle 1, Day 1		Cycle 1, Day 12		Cycle 2, Day 12		Cycle 3, Day 12	
	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)	N	Mean ± SD (%CV)
<b>FTD</b>								
AUC <sub>0-last</sub> (ng*hr/mL)	19	7044.53 ± 2411.25 (34.23)	34	23696.93 ± 7419.01 (31.31)	25	25056.38 ± 10585.99 (42.25)	9	26696.38 ± 9218.56 (34.53)
C <sub>max</sub> (ng/mL)	19	2381.21 ± 1047.61 (43.99)	34	4857.06 ± 1930.19 (39.74)	25	5458.00 ± 2269.17 (41.58)	9	5296.67 ± 2291.32 (43.26)
T <sub>max</sub> (hours) <sup>a</sup>	19	1.50 (0.53, 4.00)	34	1.97 (0.50, 8.00)	25	2.00 (0.50, 4.00)	9	2.00 (1.00, 4.00)
T <sub>1/2</sub> (hours)	19	1.42 ± 0.42	26 <sup>b</sup>	2.07 ± 0.43	19 <sup>b</sup>	2.10 ± 0.50	5 <sup>b</sup>	2.55 ± 0.79
<b>FTY</b>								
AUC <sub>0-last</sub> (ng*hr/mL)	19	3343.75 ± 897.48 (26.84)	34	5206.27 ± 2055.07 (39.47)	25	5735.54 ± 2344.99 (40.89)	9	5831.50 ± 1938.25 (33.24)
C <sub>max</sub> (ng/mL)	19	764.89 ± 201.44 (26.34)	34	678.76 ± 199.77 (29.43)	25	753.96 ± 205.31 (27.23)	9	782.89 ± 220.20 (28.13)
T <sub>max</sub> (hours) <sup>a</sup>	19	3.00 (1.00, 6.08)	34	2.00 (0.50, 8.00)	25	2.00 (1.00, 8.00)	9	3.93 (1.03, 4.00)
T <sub>1/2</sub> (hours)	19	1.76 ± 0.38	9 <sup>b</sup>	4.51 ± 0.53	6 <sup>b</sup>	3.76 ± 0.59	0 <sup>b</sup>	-
<b>TPI</b>								
AUC <sub>0-last</sub> (ng*hr/mL)	19	300.54 ± 126.92 (42.23)	34	372.13 ± 134.71 (36.20)	25	333.07 ± 124.19 (37.29)	9	298.78 ± 91.62 (30.66)
C <sub>max</sub> (ng/mL)	19	68.68 ± 29.71 (43.25)	34	69.35 ± 27.45 (39.58)	25	65.61 ± 25.46 (38.81)	9	53.70 ± 17.05 (31.76)
T <sub>max</sub> (hours) <sup>a</sup>	19	3.00 (1.02, 8.00)	34	2.01 (1.00, 8.03)	25	3.25 (1.00, 8.00)	9	4.00 (1.97, 4.08)
T <sub>1/2</sub> (hours)	16	2.10 ± 0.47	19 <sup>b</sup>	2.40 ± 0.59	12 <sup>b</sup>	2.51 ± 0.69	2 <sup>b</sup>	2.31 ± 1.03

<sup>a</sup> Median (min, max) is presented for T<sub>max</sub>.

<sup>b</sup> Due to fewer sampling time points on Day 12 (30 min, 1, 2, 4, 8 and 12 hours postdose), half-life could not be calculated for some patients.

Source: Summary of Clinical Pharmacology Studies, Table 7, Page 33

### 2.2.4.14 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?

Based on the PK data from patients in Study TPU-TAS-102-104, the inter-subject variability (CV %) was > 60% and the intra-subject variability (CV %) was <30% for trifluridine AUC<sub>0-last</sub>

and  $C_{max}$  values. Similar variability was observed for parameters of tipiracil as indicated in [Table 15](#) below.

**Table 15.** Variability in  $AUC_{0-last}$  and  $C_{max}$  Values (TPU-TAS-102-104)

	$AUC_{0-last}$	$C_{max}$
<b>FTD</b>		
Between subject (inter-subject) variance	15563809.7	5200940.8
Within subject (intra-subject) variance	1126848.2	808638.0
Geometric mean	6482.7	3547.1
Inter-subject CV(%)	60.9	64.3
Intra-subject CV(%)	16.4	25.4
<b>TPI</b>		
Between subject (inter-subject) variance	53301.4	3225.5
Within subject (intra-subject) variance	15124.3	1212.6
Geometric mean	425.4	96.8
Inter-subject CV(%)	54.3	58.6
Intra-subject CV(%)	28.9	36.0

$AUC$  units are  $ng^*hr/mL$ ;  $C_{max}$  units are  $ng/mL$ .

CV: Coefficient of variation

These are overall estimates based on the analysis of log-transformed data from TPU-TAS-102-104, from the tablet estimates from GLM model for the cross-over design with replication.

**Source:** Summary of Clinical Pharmacology Studies, Table 12, Page 42

In the PPK model, body surface area was identified as a significant covariate for volume of distribution ( $Vd/F$ ) of trifluridine and tipiracil. Creatinine clearance ( $CLcr$ ) was a significant covariate for clearance ( $CL/F$ ) of trifluridine and tipiracil, and serum albumin ( $ALB$ ) was a significant covariate for  $CL/F$  of trifluridine. Other covariates tested including age, sex, race, hepatic function parameters, and concomitant administration of OCT2 inhibitors had no clinically meaningful impact on exposure to trifluridine or tipiracil. For the final model with BSA incorporated as covariate for  $Vd/F$ , and  $CLcr$  and/or  $ALB$  incorporated as covariates for  $CL/F$ , the variabilities were reduced. The final PPK model parameters and unexplained inter-individual variability are listed in the [Table 16](#) and [Table 17](#) below.

**Table 16.** Parameter Estimates of the Final Population PK Model for Trifluridine

Parameter	Mean	RSE (%)	Shrinkage (%)
Population Mean			
Vd/F (L)	10.0	2.32	NA
CL/F (L/hr)	2.93	2.30	NA
KA (/hr)	5.43	14.8	NA
MTT (hr)	0.640	7.23	NA
CL <sub>CR</sub>	0.507	11.8	NA
ALB	-0.633	29.2	NA
BSA	0.940	16.3	NA
Inter-individual Variability			
IV Vd/F (CV%)	25.3	17.0	26.2
IV CL/F (CV%)	32.2	13.2	6.41
COV between Vd/F and CL/F	0.0401	27.9	NA
IV KA (CV%)	NA	NA	NA
IV MTT (CV%)	92.1	11.3	15.0
Residual Variability			
σ <sub>prop</sub> (%)	21.1	6.45	20.3
σ <sub>add</sub> (ng/mL)	86.3	14.5	

IV = inter-individual variability; add = additive error model; ALB = albumin; BSA = body surface area; CL<sub>CR</sub> = creatinine clearance; CL/F = apparent oral clearance; COV = covariance; CV = coefficient of variation; KA = absorption rate constant; MTT = mean transit time; η = inter-individual residual; NA = not applicable; nt = number of transit compartment; σ = variance of residual error; prop = proportional residual error model; RSE = relative standard error; Vd/F = apparent distribution volume.

1-Compartment model with transit absorption model (nt=4)

$$Vd/F = 10.0 \times (BSA/1.81)^{0.94} \times \exp(\eta_{Vd/F})$$

$$CL/F = 2.93 \times (CLCR/103)^{0.507} \times (ALB/3.90)^{-0.633} \times \exp(\eta_{CL/F})$$

Source: Study 12DA25, Table 9.3.3-1.

Source: Table 14 summary of clinical pharmacology, Page 44

**Table 17.** Parameter Estimates of the Final Population PK Model for Tipiracil

Parameter	Mean	RSE (%)	Shrinkage (%)
Population Mean			
Vd/F (L)	192	8.49	NA
V2 (L)	240	16.0	NA
CL/F (L/hr)	88.7	2.90	NA
Q (L/hr)	16.0	12.8	NA
KA (/hr)	0.845	8.28	NA
MTT (hr)	0.867	5.85	NA
CL <sub>CR</sub>	0.592	15.1	NA
BSA	1.46	25.3	NA
Inter-individual Variability			
IV Vd/F (CV%)	62.7	16.3	21.4
IV CL/F (CV%)	44.3	14.7	4.58
COV between Vd/F and CL/F	0.137	23.9	NA
IV KA (CV%)	NA	NA	NA
IV MTT (CV%)	72.9	12.4	12.2
Residual Variability			
σ <sub>prop</sub> (%)	27.1	4.24	20.3

IV = inter-individual variability; BSA = body surface area; CL<sub>CR</sub> = creatinine clearance; CL/F = apparent oral clearance; COV = covariance; CV = coefficient of variation; KA = absorption rate constant; MTT = mean transit time; η = inter-individual residual; NA = not applicable; nt = number of transit compartment; σ = variance of residual error; prop = proportional residual error model; Q = clearance between compartments; RSE = relative standard error; Vd/F = apparent distribution volume of central compartment; V2 = apparent distribution volume of peripheral compartment.

2-compartment model with transit absorption model (nt=4).

$$Vd/F = 192 \times (BSA/1.81)^{1.46} \times \exp(\eta_{Vd/F})$$

$$CL/F = 88.7 \times (CLCR/103)^{0.592} \times \exp(\eta_{CL/F})$$

Source: Study 12DA25, Table 9.3.6-1.

Source: Table 15 summary of clinical pharmacology, Page 45

## 2.3 INTRINSIC FACTORS

### **2.3.1 *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?***

Population pharmacokinetic analysis (n=239) indicated that body size and renal function are the primary intrinsic factors that affect the exposure to trifluridine or tipiracil after dosing of TAS-102. Oral clearance of trifluridine also negatively correlated with serum albumin probably due to the high protein binding of trifluridine. Other covariates tested including age, sex, race, hepatic function parameters representing normal function to mild hepatic impairment, and concomitant administration of OCT2 inhibitor had no clinically meaningful impact on exposure to trifluridine or tipiracil.

#### **2.3.1.1 *Age***

The age of the patients ranged from 33 to 82 years old in the dataset analyzed (n=239, mean of 60 years, and median of 61 years). Age was not a significant covariate for PK parameters of either trifluridine or tipiracil. Exposures of trifluridine and tipiracil are not expected to be affected by age.

#### **2.3.1.2 *Sex***

The population PK dataset included more men (59%) than women (41 %). Although sex was selected as a statistically significant covariate on Vd/F of trifluridine in the forward addition procedure of covariate modeling, it was no longer significant once BSA was incorporated into the model. The apparent inter-individual difference on Vd/F of trifluridine seen for sex is attributable to the difference in body size, which has been adjusted by BSA based dosing of TAS-102.

#### **2.3.1.3 *Race***

The dataset consisted of 61% White, 26% Asian (mainly Japanese) patients and 13% others. Race was not a significant covariate for PK parameters of either trifluridine or tipiracil. Exposures of trifluridine and tipiracil are not expected to be affected by Race.

#### **2.3.1.4 *Body Size***

Body surface area (BSA) ranged from 1.1 to 2.48 m<sup>2</sup> in the dataset analyzed (n=239, mean of 1.82 m<sup>2</sup>, and median of 1.81 m<sup>2</sup>). BSA was a significant covariate for Vd/F in both final models for trifluridine and tipiracil. Some apparent differences of inter-individual residuals seen in race and sex might be attributed to the confounding with BSA because race and sex were not included in the models. The BSA based dosing of TAS-102 is justified to reduce the variability of exposure of trifluridine and tipiracil.

### 2.3.1.5 Renal Impairment

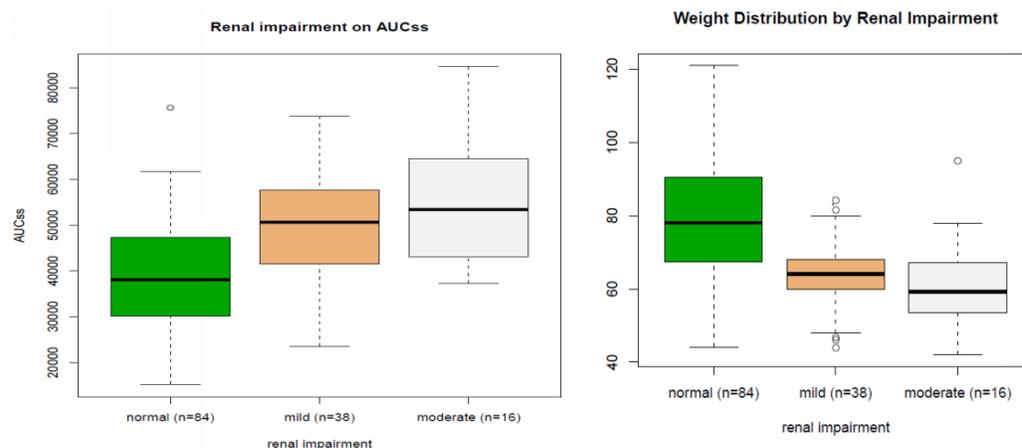
No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the PK of TAS-102. Based on the population PK analysis, estimated creatinine clearance (CL<sub>cr</sub>) was a significant covariate for clearance of trifluridine and tipiracil following oral administration of TAS-102. In Study RECURSE, the mean values of AUC at steady state for trifluridine were 31% higher in patients with mild renal impairment (CL<sub>cr</sub> = 60-89 mL/min, n =38) and 43% higher in patients with moderate renal impairment (CL<sub>cr</sub> = 30 to 59 mL/min, n= 16) than that for patients with normal renal function (CL<sub>cr</sub> ≥ 90 mL/min, n=84). Similar effect of renal impairment on the tipiracil exposure was observed (34% higher in patients with mild and 68% higher in patients with moderate renal impairment than that in patients with normal renal function) (Table 18). The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment (CL<sub>cr</sub> < 30 mL/min) or end-stage renal disease. The increased exposures of trifluridine and tipiracil in patients with mild to moderate renal impairment might be confounded by the relatively smaller body weights in the mild (median body weight=64 kg, n= 38) and moderate (median body weight=59 kg, n=16) renal impaired patients when compared to patients with normal renal function (median body weight=78 kg, n=84) (Figure 7). Since tipiracil is a PK modulator that enhances the systemic exposure of trifluridine by inhibiting TPase, the increased exposure of trifluridine in patients with mild and moderate renal impairment could be the secondary effect mediated by the increased tipiracil exposures leading to increased inhibition of trifluridine metabolism (via TPase) in the same patients with renal impairment.

**Table 18.** Summary of Daily AUC for Each Renal Function Subgroup (PK Population in Study RECOURSE)

Renal Impairment Based on CLcr	Analyte PK Parameter Unit Period Method	FTD	TPI HCl
		Daily AUC ng*hr/mL Day 12 Pop-PK	Daily AUC ng*hr/mL Day 12 Pop-PK
Normal (CLcr >=90 mL/min)	n	84	84
	Mean	38812.0	630.7
	SD	10905.3	300.5
	CV	28%	48%
Mild Impairment (CLcr 60-89 mL/min)	n	38	38
	Mean	50177.8	825.9
	SD	11835.6	343.0
	CV	24%	42%
	Ratio of Geometric Mean to the Normal Group Estimate (95% CI)	1.31 (1.17 - 1.46)	1.34 (1.13 - 1.59)
Moderate Impairment (CLcr 30-59 mL/min)	n	16	16
	Mean	54898.0	1060.9
	SD	13675.8	616.5
	CV	25%	58%
	Ratio of Geometric Mean to the Normal Group Estimate (95% CI)	1.43 (1.22 - 1.68)	1.65 (1.29 - 2.11)

Source: Table 1, Sponsor's response to the IR of analysis of renal function effect in Study RECOURSE

**Figure 7.** Effect of Renal Impairment on AUCs of Trifluridine in Study RECOURSE

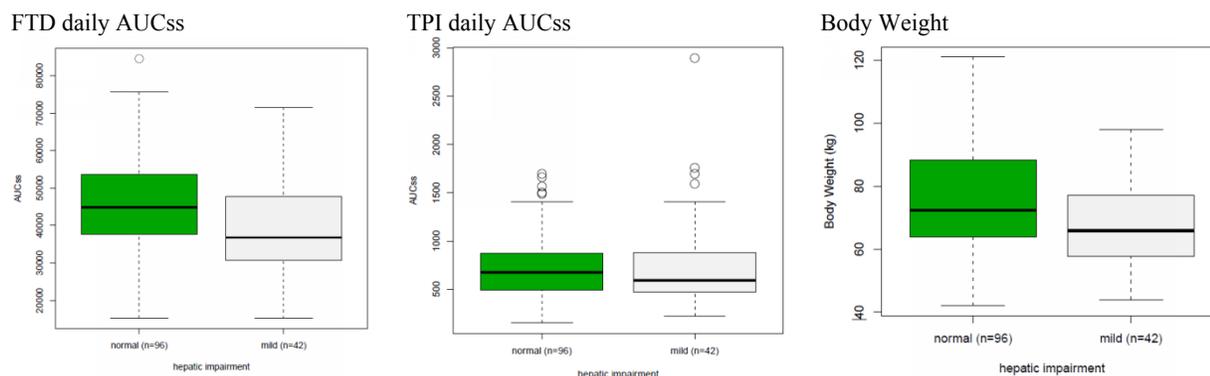


Reviewer's analysis based on data set adpk.xpt provided from Study RECOURSE.

### 2.3.1.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of TAS-102. Based on the population PK analysis of Study RECOURSE with data from patients with normal liver function (total bilirubin (TB) and AST  $\leq$  the upper limit of normal (ULN), n= 96) and patients with mild hepatic impairment (TB  $\leq$ ULN and AST  $>$  ULN or  $1 \times$ ULN  $<$  TB  $<$  to  $1.5 \times$  ULN and any AST, n=42), liver function parameters including ALT, AST, ALP, and total bilirubin were not covariates for PK parameters of either trifluridine or PTI. Mild hepatic impairment had no clinically meaningful effect on exposure of either trifluridine or tipiracil as compared to patients with normal liver function (Figure 8). Patients with moderate ( $1.5 \times$ ULN  $\leq$  TB  $<$   $3 \times$  ULN and any AST) or severe (TB  $\geq 3 \times$  ULN and any AST) hepatic impairment were not enrolled in Study RECOURSE. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with moderate to severe hepatic impairment. The exposure of trifluridine in patients with mild hepatic impairment might be confounded by the body weight or different TPase level in the patients with mild impaired hepatic function (median body weigh=66 kg, n= 42) when compared to the patients with normal hepatic function (median body weigh=72 kg, n= 96).

**Figure 8.** Effect of Hepatic Impairment on AUCs of Trifluridine and Tipiracil in Study RECOURSE



Reviewer's analysis based on data set adpk.xpt provided from Study RECOURSE.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dose regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

The BSA based dosing of TAS-102 is justified as it reduces the variability of exposure of trifluridine and tipiracil. No clinically meaningful PK differences have been identified for other tested covariates including age, sex, and race. Dedicated renal impairment study and hepatic impairment study are proposed as post marketing requirements (PMRs) to further verify the effects of organ impairment on the exposure, tolerability and safety for TAS-102.

### **2.3.2.1 Elderly Patients**

Age was not identified as a significant covariate influencing TAS-102 PK based on a population PK analysis. In Study RECOURSE, 533 patients received TAS-102; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of TAS-102 based on age.

Compared to patients younger than 65 years, patients 65 years of age or older who received TAS-102 had a higher incidence of the following AEs: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

### **2.3.2.2 Sex**

The effect of sex was evaluated in men (n=141, 59%) and women (n=98, 41%). The popPK analysis did not identify sex as a significant covariate influencing trifluridine or tipiracil PK. Refer to [Section 2.3.1.2](#)

### **2.3.2.3 Race**

The effect of race was evaluated in White (n=146, 61%), Asian (mainly Japanese) (n=93, 26%) and 17% others. The popPK analysis did not identify race as a significant covariate influencing trifluridine or tipiracil PK. Refer to [Section 2.3.1.3](#)

### **2.3.2.4 Renal Impairment**

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the PK of TAS-102. Refer to [Section 2.3.1.5](#)

In Study RECOURSE, patients with moderate renal impairment (CL<sub>cr</sub> = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CL<sub>cr</sub> ≥ 90 mL/min, n= 306) and patients with mild renal impairment (CL<sub>cr</sub> = 60 to 89 mL/min, n= 178).

No dose adjustment to the starting dose of Lonsurf is recommended in patients with mild or moderate renal impairment (CL<sub>cr</sub> of 30 to 89 mL/min); however patients with mild or moderate renal impairment should be monitored for increased toxicity. No patients with severe renal impairment (CL<sub>cr</sub> <30 mL/min) were enrolled in Study RECOURSE. A dedicated renal impairment is currently on going and will be submitted as a PMR study.

### **2.3.2.5 Hepatic Impairment**

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of TAS-102. No dose adjustment is recommended for patients with mild hepatic impairment (TB ≤ ULN and AST >ULN or TB < 1 to 1.5 ×ULN and any AST). Patients with

moderate (TB > 1.5 to 3 ×ULN and any AST) or severe (TB > 3×ULN and any AST) hepatic impairment were not enrolled in Study RECOURSE. A dedicated hepatic impairment study is currently ongoing and will be submitted as a PMR study. Refer to [Section 2.3.1.6](#)

#### ***2.3.2.6 What pregnancy and lactation use information is in the application?***

According to the proposed labeling, it is not known whether Lonsurf and/or its metabolites are excreted in human milk. In nursing rats, trifluridine, tipiracil, and/or their metabolites have been demonstrated to be secreted into breast milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lonsurf and any potential adverse effects on the breastfed child from Lonsurf or from the underlying maternal condition.

## **2.4 EXTRINSIC FACTORS**

### ***2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?***

No dedicated studies were conducted to evaluate the impact of extrinsic factors (drugs, herbal products, smoking, and alcohol use) on the PK of TAS-102. Refer to the [section 2.5.3](#) for the food effect on the exposure of LONSURF.

### ***2.4.2 What are the drug-drug interactions?***

#### ***2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?***

No. See below.

#### ***2.4.2.2 Is the drug a substrate of CYP enzymes?***

No. Trifluridine is a substrate of thymidine phosphorylase, and is not metabolized by cytochrome P450 (CYP) enzymes. Tipiracil is not metabolized in either human liver S9 or cryopreserved hepatocytes.

#### ***2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?***

No. In vitro studies indicated that trifluridine, tipiracil, and FTY did not inhibit the human CYP enzymes and had no inductive effect on human CYP1A2, CYP2B6 or CYP3A4/5.

#### ***2.4.2.4 Is the drug an inhibitor and/or an inducer of transporters?***

FTD was not an inhibitor of or substrate for human uptake and efflux transporters. Tipiracil was a substrate and an inhibitor of OCT2 *in vitro* at concentrations 3-fold or higher than the observed plasma  $C_{max}$  in clinical studies. The population PK analysis suggested that concomitant administration of OCT2 inhibitors (n=24) had no effect on the PK parameters of trifluridine and tipiracil.

**2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

None.

**2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

No. The influence of thymidine analogues on PK parameters of trifluridine was not able to be examined because there were no patients who took other thymidine analogues concomitantly with TAS-102. In addition, 10% of overall patients received concomitant OCT2 inhibitors (famotidine, metformin, and ranitidine) in the clinical studies. The influence of OCT2 inhibitors on PK parameters such as Vd/F, CL/F, and mean transit time on tipiracil was examined using the base model of tipiracil. These OCT2 inhibitors did not demonstrate any clinically meaningful effects on the PK parameters of tipiracil.

**2.4.2.7 What other co-medications are likely to be administered to the target population?**

Not Applicable

**2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

None.

**2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?**

None. Refer to [Section 2.4.2.6](#)

**2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

None.

**2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?**

None.

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

The Applicant classifies trifluridine and tipiracil as BCS class III compounds based on data showing low membrane permeability across Caco-2 cell monolayers and high solubility in buffer solutions ranging in pH values from 1 to 7.5 (refer to [Section 2.1.1](#)).

Both the Early Clinical Trial Material (CTM) Formulation and the Late CTM Formulation showed rapid dissolution (90% dissolved in 15 minutes) in water and buffered media of pH 1.2 to 6.8 ([Table 19](#)). Furthermore, the 20 mg strength of Late CTM Formulation also showed similar rapid dissolution in FaSSIF (fasted state simulated intestinal fluid, pH 6.5) and FeSSIF (fed state simulated intestinal fluid, pH 5.0) as shown in [Table 20](#). The formulation differences

between the Early CTM Formulation and the Late CTM Formulation did not affect the dissolution of trifluridine and tipiracil. Refer to the CMC reviews.

**Table 19.** Dissolution Test Results, Mean Quantities (Percent) of Trifluridine and Tipiracil Released at 15 min from Early CTM Formulation and Late CTM Formulation in Various pH Media at 37°C

Product and Dose of FTD		Water (n = 12)		pH 1.2 (n = 12)		pH 4.5 (n = 12)		pH 6.8 (n = 12)	
		15 mg	20 mg	15 mg	20 mg	15 mg	20 mg	15 mg	20 mg
Early CTM Formulation <sup>1</sup>	FTD	(b) (4)							
	TPI								
Late CTM Formulation <sup>2</sup>	FTD								
	TPI								

<sup>1</sup> Tablet formulation used in the Phase 1 and Phase 2 programs.

<sup>2</sup> Tablet formulation used in the Phase 1, 2, and 3 programs.

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 7, Page 15

**Table 20.** Mean Quantities (Percent) of Trifluridine and Tipiracil Released at 15 min from Early CTM Formulation and Late CTM Formulation 20 mg Tablets in Biorelevant Media at 37°C

Product and Dose of FTD		FaSSIF at pH 6.5 (n = 3)		FeSSIF at pH 5.0 (n = 3)	
		15 mg	20 mg	15 mg	20 mg
Early CTM Formulation <sup>1</sup>	FTD	(b) (4)			
	TPI				
Late CTM Formulation <sup>2</sup>	FTD				
	TPI				

FaSSIF = fasted state simulated intestinal fluid; FeSSIF = fed state simulated intestinal fluid

<sup>1</sup> Tablet formulation used in the Phase 1 and Phase 2 studies.

<sup>2</sup> Tablet formulation used in the Phase 1 and Phase 3 studies.

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 8, Page 16

### 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

#### *Formulations Used to Support the Application:*

The to-be-marketed (TBM) formulation tablets are identical to the Late CTM formulation with the exception of (b) (4), which were used in Study TPU-TAS-102-102, Study TPU-TAS-102-103, Study TPU-TAS-102-104, and Study TPU-TAS-102-301 (RECOURSE). The Early CTM formulations were used in Study J001-10040010, Study J001-10040030, Study TPU-TAS-102-101 and Study J001-10040040. Summary of formulation characteristics for TAS-102 film coated tablets is listed in Table 21. The formulation assessment according to the guidance given in SUPAC-IR is listed in Table 22. These were Level 1 changes from Early CTM formulation to

Later CTM formulation. Based on these criteria, no in vivo bioequivalence studies are required and the data derived from studies conducted using each formulation can be directly compared. Refer to CMC review.

**Table 21.** Summary of Formulation Characteristics for TAS-102 Film Coated Tablets

Component	Function	Early CTM Formulation Studies J001-10040010, J003-10040030, J004-10040040, and TPU-TAS-102-101		Late CTM Formulation Studies TPU-TAS-102-102, TAS-102-103, TPU-TAS-102-104, and TPU-TAS-102-301		To-be-marketed Formulation	
		FTD/TPI (15/7.065)	FTD/TPI (20/9.42)	FTD/TPI (15/7.065)	FTD/TPI (20/9.42)	FTD/TPI (15/7.065)	FTD/TPI (20/9.42)
(b) (4) FTD	Active	15 mg	20 mg	15 mg	20 mg	15 mg	20 mg
TPI	Active	7.065 mg	9.42 mg	7.065 mg	9.42 mg	7.065 mg	9.42 mg
Lactose monohydrate		(b) (4)					
Pregelatinized starch							
Stearic acid							
(b) (4)							
Hypromellose (b) (4)							
Polyethylene glycol							
Titanium dioxide							
Red ferric oxide							
Magnesium stearate							
(b) (4)							
(b) (4)							
Total							
Printing <sup>1</sup>							
Shape and Size							
Manufacturing site		Tokushima		Tokushima		Kitajima	
Charge-in (Tablets)		(b) (4)					

CTM = clinical trial material; FTD = trifluridine; TPI = tipiracil

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 2, Page 10

**Table 22.** TAS-102 Tablet Formulations and Change Levels According to SUPAC-IR

Parameter	Difference Between Early CTM Formulation and Late CTM Formulation	SUPAC IR Change Level
Components and composition	New trace excipients (red ferric oxide and magnesium stearate) were added (b) (4) to Late CTM Formulation.	Level 1
Changes in batch size	Change in batch size is up to (b) times	Level 1
Manufacturing	Change to alternative equipment of the same design and operating principles of the same or of a different capacity	Level 1

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 4, Page 12

*Relative Bioavailability of the Late CTM Tablet Formulation to Oral Solution:*

In study TPU-TAS-102-104, a randomized cross-over bioavailability study was conducted to evaluate the relative bioavailability of TAS-102 tablets compared to an oral solution in patients with advanced solid tumors. Following an overnight fast of at least 8 hours, 46 patients were treated with 60 mg TAS-102 (20 mg × 3 tablets) or oral solution (containing equivalent amounts of trifluridine and tipiracil) according to randomized sequence (Sequence A or B). Patients

randomized to Sequence A received TAS-102 tablets in Period 1, oral solution in Period 2, and oral solution in Period 3; whereas patients randomized to Sequence B received TAS-102 oral solution in Period 1, TAS-102 tablets in Period 2, and TAS-102 tablets in Period 3. Each period was separated by a 7-day washout period. Of the 46 patients treated, 38 (82.6%) were included in the Crossover BA PK population, and 45 (97.8%) were included in the All PK population (Table 23).

**Table 23.** Study Populations in the Relative Bioavailability Study TPU-TAS-102-104

	Number (%) of Patients		
	Sequence A <sup>a</sup>	Sequence B <sup>b</sup>	Total BA PK
<b>Patients in Safety Population</b>	23 (100)	23 (100)	46 (100)
<b>Evaluable For BA PK</b>	21 (91.3)	17 (73.9)	38 (82.6)
<b>Not Evaluable for BA PK</b>	2 (8.7)	6 (26.1)	8 (17.4)
At least 2 periods not available	0	1 (4.3) <sup>c</sup>	1 (2.2)
Fasting conditions not met	1 (4.3)	3 (13.0)	4 (8.7)
Data not available	1 (4.3) <sup>d</sup>	0	1 (2.2)
Other	0	2 (8.7) <sup>e</sup>	2 (4.3)

<sup>a</sup> Tablet/oral solution/oral solution

<sup>b</sup> Oral solution/tablet/tablet

<sup>c</sup> Patient 401-031 discontinued after Period 1 due to clinical disease progression (Appendix 16.2.1.1).

<sup>d</sup> Patient 401-026 was excluded for Period 2 due to samples not collected at multiple time points (Appendix 16.2.2.3); and did not have PK assessment during Period 3 (discontinued prior to dosing due to SAE of hyperbilirubinaemia [Appendix 16.2.1.1]).

<sup>e</sup> Patient 402-005 was excluded for Periods 2 and 3 due to inability to determine adequate AUC; Patient 402-017 was excluded for all 3 periods since source documents indicated that the patient had undergone partial gastrectomy (Appendix 16.2.1.5.1).

Source: CSR of Study TPU-TAS-102-104, Table 9, Page 55

The statistical analysis showed that the relative bioavailability of tablets compared to oral solution based on the ratio of geometric means for  $AUC_{0-last}$  was 100% (90% CI: 0.93-1.09) for trifluridine and 96% (90% CI: 0.86-1.07) for tipiracil (Table 24). The corresponding 90% CIs for  $AUC_{0-inf}$  and  $AUC_{0-last}$  were within the 0.80 to 1.25 boundary for demonstration of bioequivalence. The results were similar for the trifluridine metabolites, FTY and 5-CU. Due to slightly delayed absorption for the tablet, the geometric mean value of trifluridine  $C_{max}$  was lower for the TAS-102 tablet than for the oral solution (relative bioavailability of 86% [90% CI: 0.79-0.95]).

**Table 24.** Statistical Analysis of Relative Bioavailability (BA PK Population in Study TPU-TAS-102-104)

Analyte Parameter	Tablet Geometric Mean <sup>1</sup>	Oral Solution Geometric Mean <sup>1</sup>	Ratio of Geometric Means (Tablet/Oral solution)	
			Estimate	(90% CI)
<b>FTD</b>				
AUC <sub>0-last</sub> (ng*hr/mL)	6482.74	6454.59	1.004	(0.926 - 1.089)
C <sub>max</sub> (ng/mL)	3547.07	4115.58	0.862	(0.786 - 0.945)
AUC <sub>0-inf</sub> (ng*hr/mL)	6572.53	6581.22	0.999	(0.918 - 1.087)
<b>TPI</b>				
AUC <sub>0-last</sub> (ng*hr/mL)	425.39	442.94	0.960	(0.859 - 1.073)
C <sub>max</sub> (ng/mL)	96.84	95.74	1.012	(0.885 - 1.156)
AUC <sub>0-inf</sub> (ng*hr/mL)	448.45	457.82	0.980	(0.865 - 1.109)
<b>FTY</b>				
AUC <sub>0-last</sub> (ng*hr/mL)	3145.52	3127.11	1.006	(0.959 - 1.055)
C <sub>max</sub> (ng/mL)	924.74	988.14	0.936	(0.881 - 0.994)
AUC <sub>0-inf</sub> (ng*hr/mL)	3226.61	3203.54	1.007	(0.961 - 1.055)
<b>5-CU</b>				
AUC <sub>0-last</sub> (ng*hr/mL)	12.74	12.35	1.031	(0.921 - 1.154)
C <sub>max</sub> (ng/mL)	2.36	2.36	1.002	(0.941 - 1.068)
AUC <sub>0-inf</sub> (ng*hr/mL)	--- <sup>2</sup>	--- <sup>2</sup>	---	---

<sup>1</sup> Derived using the least-square means from the crossover model with replication.

<sup>2</sup> Could not be determined due to small sample size.

Source: CSR of Study TPU-TAS-102-104, Table 14, Page 64

### 2.5.3 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

A food effect study was conducted in Japanese patients with solid tumors (excluding those who had gastric cancer or a history of gastrectomy) using Early CTM tablets formulation of TAS-102 (Study J004-10040040). A total of 16 patients were enrolled and received single doses of 35 mg/m<sup>2</sup> TAS-102 under two conditions with washout period of at least 4 days, assigned in random order: the fasting condition and after a high-fat, high calorie meal. The contents of meals were determined with reference to the FDA's guidance and the required number of calories was adjusted according to the mean body weight ratio between U.S. and Japanese patients.

Food effects were assessed using ANOVA (Analysis of Variance) to calculate the geometric mean ratio (fed/fasting) and its 90% Confidence Interval (90% CI) of the C<sub>max</sub>, AUC<sub>0-12h</sub>, and AUC<sub>0-inf</sub>. In addition, food effects on T<sub>max</sub> were assessed by the Wilcoxon signed-rank test. Results are listed in Table 25. The C<sub>max</sub> of trifluridine was decreased by 40% and C<sub>max</sub> and AUC of tipiracil were decreased by 45% in the fed state compared to the fasting state, and the corresponding 90% CI of the geometric mean ratios for C<sub>max</sub> of trifluridine, C<sub>max</sub> of tipiracil, and AUC of tipiracil were not in the 0.80 to 1.25 range for bioequivalence. There were no significant differences in AUC of trifluridine and T<sub>max</sub> of trifluridine or tipiracil after administration in fasting or fed states.

**Table 25.** Geometric Mean Ratio (Fed/Fasting) and 90% Confidence Interval of Trifluridine and Tipiracil Pharmacokinetic Parameters (Study J004-1040040)

PK Parameter	FTD		TPI	
	Geometric Mean Ratio (Fed/Fasting)	90% Confidence Interval [Lower-Upper]	Geometric Mean Ratio (Fed/Fasting)	90% Confidence Interval [Lower-Upper]
C <sub>max</sub>	0.6074	[0.5037 – 0.7323]	0.5578	[0.4372 – 0.6576]
AUC <sub>0-t</sub>	0.9561	[0.8566 – 1.0671]	0.5526	[0.4802 – 0.6358]
AUC <sub>0-12</sub>	0.9560	[0.8566 – 1.0670]	0.5526	[0.4802 – 0.6358]
AUC <sub>0-inf</sub>	0.9559	[0.8556 – 1.0680]	0.5581	[0.4802 – 0.6392]

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 12, Page 26

**2.5.4** *When would a fed BE study be appropriate and was one conducted?*

Not applicable.

**2.5.5** *How do dissolution conditions and specifications ensure in vivo performance and quality of the product?*

The dissolution test conditions are listed in [Table 26](#) below. No statistical analyses of correlations between in vitro and in vivo dissolution characteristics were performed. The drug product rapidly releases under the conditions testing for dissolution parameters that mimic physiological conditions (refer to [Section 2.5.1](#)). Refer to CMC reviews.

**Table 26.** Dissolution Test Conditions

	Dissolution Medium Volume (mL)	Apparatus (USP)	Rotation Speed (rpm)	Temperature (°C)	Number of vessels	Sampling Time (minutes)
pH 1.2 <sup>1</sup>	900	2 (Paddle)	50	37 ± 0.5	12	5, 10, 15, 20
pH 4.5 <sup>2</sup>	900	2 (Paddle)	50	37 ± 0.5	12	5, 10, 15, 20
pH 6.8 <sup>3</sup>	900	2 (Paddle)	50	37 ± 0.5	12	5, 10, 15, 20
Water	900	2 (Paddle)	50	37 ± 0.5	12	5, 10, 15, 20
FaSSIF <sup>4</sup>	500	2 (Paddle)	50	37 ± 0.5	3	15
FeSSIF <sup>5</sup>	900	2 (Paddle)	50	37 ± 0.5	3	15

JP = Japanese Pharmacopeia; rpm = revolutions per minute; USP = United States Pharmacopeia

<sup>1</sup> Simulated Gastric Fluid without enzymes (USP)

<sup>2</sup> Acetate buffer (USP)

<sup>3</sup> 2nd fluid for the dissolution test (pH 6.8 phosphate buffer, JP 16)

<sup>4</sup> fasted state simulated intestinal fluid

<sup>5</sup> fed state simulated intestinal fluid

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 12, Page 26

**2.5.6** *If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?*

Not applicable. Same formulation was used for TAS-102 strength 15 mg and 20 mg (expressed as mg of trifluridine per tablet). Refer to CMC review.

**2.5.7** *If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

Not applicable.

**2.5.8** *If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?*

Not applicable.

**2.5.9** *What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?*

None.

## 2.6 ANALYTICAL SECTION

### **2.6.1 *How are the active moieties identified and measured in the plasma and the other matrices?***

The parent compound trifluridine, its major metabolite FTY, and the PK modulating component in the combination drug, tipiracil were measured in plasma and urine using validated liquid chromatography-mass spectrometry (LC-MS/MS).

### **2.6.2 *Which metabolites have been selected for analysis and why?***

The major metabolite FTY has been selected for analysis in urine and plasma after dosing of TAS-102. Bioanalysis methods for other minor metabolites including 6-HMU, dThd, 5-CU and 5-CdUrd were also validated for quantitation in plasma and/or urine after dosing of TAS-102.

### **2.6.3 *For all moieties measured is free, bound or total measured?***

The dose of TAS-102 was expressed on the basis of the milligram content of trifluridine, and concentrations of trifluridine and metabolites were calculated as for the free form. For tipiracil, the concentrations were measured as the tipiracil free form, and the measured concentrations were converted to the equivalent of the hydrochloride form before being subjected to PK analysis.

### **2.6.4 *What bioanalytical methods are used to assess concentrations?***

Validated LC-MS/MS methods were used to measure the concentrations of the moieties in human plasma and urine. Validation details are provided in [Table 27](#) for quantitation of trifluridine, FTY, and tipiracil in plasma and urine. Details for the validation for quantitation of 6-HMU in plasma and urine, dThd in plasma, 5-CU, and 5-CdUrd in plasma and urine are provided in [Table 28](#).

**Table 27. Results of Validation of the Analytical Methods for Trifluridine, FTY and Tipiracil in Human Plasma and Urine**

Source (Report Nos):		P04-10402, P04-10405, P12-10413, P12-10414, P13-10422				P04-10403, P04-10405, P12-10413, P12-10414, P13-10422	
Location in NDA		5.3.1.4				5.3.1.4	
Biological sample		Plasma		Urine		Plasma	Urine
Analyte		FTD	FTY	FTD	FTY	TPI	TPI
Anticoagulant		Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin
Sample processing (extraction method)		Liquid-liquid	Liquid-liquid	Liquid-liquid	Liquid-liquid	Solid phase	Solid phase
Analytical method		LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Calibration range (ng/mL)		5 to 5000	5 to 5000	200 to 200,000	200 to 200,000	0.2 to 200	200 to 100,000
Lower quantitation limit (ng/mL)		5	5	200	200	0.2	200
Within-day reproducibility	Precision <sup>1</sup> (%)	1.4 to 6.2	1.5 to 12.7	1.3 to 10.0	1.6 to 7.7	2.1 to 13.4	1.0 to 4.6
	Accuracy <sup>2</sup> (%)	-4.0 to 3.0	-7.2 to 7.0	-5.0 to 2.8	-2.5 to 3.8	-3.0 to 3.8	2.0 to 5.6
Between-day reproducibility	Precision <sup>1</sup> (%)	1.8 to 6.7	1.7 to 10.7	1.4 to 9.5	1.9 to 6.8	2.1 to 9.6	1.9 to 5.2
	Accuracy <sup>2</sup> (%)	-4.0 to 2.4	-7.7 to 6.0	-0.4 to 5.5	-2.5 to 2.8	1.0 to 4.0	2.0 to 5.9
Stability	Freezing and thawing	6 cycles	6 cycles	6 cycles	6 cycles	6 cycles	6 cycles
	Short-term (room temp)	24 hrs	24 hrs	24 hrs	24 hrs	24 hrs	24 hrs
	In auto-sampler	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)
	-15°C <sup>3</sup>	370 days	370 days	370 days	370 days	366 days	366 days
	-65°C <sup>4</sup>	362 days	362 days	373 days	189 days	370 days	369 days
Testing facility		(b) (4)					
Relevant clinical Study Nos.		J001-10040010, J004-10040040, TPU-TAS-102-102, TAS-102-103, TPU-TAS-102-104, and TPU-TAS-102-301					

FTD = trifluridine; FTY =5-trifluoromethyluracil; LC/MS/MS = liquid chromatography/tandem mass spectroscopy; TPI = tipiracil.

<sup>1</sup> Coefficient of variation

<sup>2</sup> Relative error.

<sup>3</sup> Performed in Studies P04-10402, P04-10405, P12-10413

<sup>4</sup> Performed in Study P12-10414

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 10, Page 22

**Table 28.** Results of Validation of the Analytical Methods for 6-HMU, dThd, 5-CU and 5-CdUrd in Human Plasma and Urine

Source (Report Nos):	P06-18601	P06-18602	P04-10404, P04-10405	11DA03, 11DA04	P12-32101		
Location in NDA	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4		
Biological sample	Plasma	Urine	Plasma	Plasma	Plasma	Urine	
Analyte	6-HMU	6-HMU	dThd	5-CU	5-CU, 5-CdUrd	5-CU, 5-CdUrd	
Anticoagulant	Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin	Sodium heparin	
Sample processing (extraction)	Liquid-liquid	Liquid-liquid	Solid phase	Liquid-liquid	Liquid-liquid	Liquid-liquid	
Analytical method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	
Calibration range (ng/mL)	1.00 to 500	50.0 to 50,000	0.4 to 200	1.00 to 200	1.00 to 200	200 to 200,000	
Lower quantitation limit (ng/mL)	1.00	50.0	0.4	1.00	1.00	200	
Within-day reproducibility	Precision <sup>1</sup> (%)	1.6 to 5.5	0.5 to 6.4	1.9 to 13.3	1.1 to 6.2	0.6 to 5.4, 1.4 to 6.9	1.3 to 4.3, 1.2 to 14.1
	Accuracy <sup>2</sup> (%)	-4.0 to 2.0	-2.0 to 10.8	-4.0 to 0.0	-5.5 to -2.5	0.5 to 11.0, -7.5 to 12.5	-10.0 to 3.8, -5.6 to 10.6
Between-day reproducibility	Precision <sup>1</sup> (%)	2.6 to 7.2	1.6 to 5.7	2.3 to 10.2	2.6 to 10.4	2.0 to 4.6, 4.8 to 8.5	3.5 to 4.7, 3.2 to 8.9
	Accuracy <sup>2</sup> (%)	-1.2 to 4.8	-3.0 to 6.0	-0.8 to 0.3	-9.0 to -4.4	2.0 to 8.0, -0.7 to 5.5	-7.2 to 0.6, -1.9 to 5.6
Stability	Freezing and thawing	6 cycles	6 cycles	6 cycles	3 cycles	6 cycles	6 cycles
	Short-term (room temp)	24 hrs	24 hrs	8 hrs (ice-bath)	4 hrs	24 hrs	24 hrs
	In auto-sampler	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)	48 hrs (10°C)	77 hrs (10°C)	74 hrs (10°C)
	-15°C to -65°C	42 days	39 days	368 days	185 days	366 days	366 days
Testing facility		(b) (4)		TPC		(b) (4)	
Relevant Clinical Study Nos.		J001-10040010		J004-10040040		TPU-TAS-102-104	

5-CU = 5-carboxyuracil; 5-CdUrd = 5-carboxy-2'-deoxyuridine; 6-HMU = 6-hydroxymethyluracil; dThd = thymidine; LC/MS/MS = liquid chromatography/tandem mass spectroscopy; TPC = Taiho Pharmaceutical Company, Ltd.; (b) (4)

<sup>1</sup> Coefficient of variation

<sup>2</sup> Relative error

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 11, Page 23

#### 2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

Refer to Table 27 and Table 28 for the range of the standard curves. The standard curve ranges are from 5 to 5000 ng/mL for trifluridine and its metabolite FTY, and 0.2 to 200 ng/mL for tipiracil in plasma. The equations of the regression line of calibration standards were carried out by the  $1/x^2$ . The standard curve ranges are adequate for the purposes of determining plasma concentrations of trifluridine, FTY and tipiracil in the clinical studies.

#### 2.6.4.2 What are the lower and upper limits of quantification?

Refer to Table 27 and Table 28. The LLOQ is 5.00 ng/mL for trifluridine and 0.200 ng/mL for tipiracil; The ULOQ is 5000 ng/mL for trifluridine and 200 ng/mL for tipiracil.

#### 2.6.4.3 What are the accuracy, precision and selectivity at these limits?

Refer to Table 27 and Table 28 for the accuracy and precision for the LLOQ. The mean %bias and %CV of calibration standards and quality controls for validation of the bioanalytical method were  $\leq 15\%$ , and are acceptable based on the 2013 FDA Bioanalytical Method Validation Guidance.

**2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)**

Refer to [Table 27](#) and [Table 28](#).

**2.6.4.5 What is the QC sample plan?**

Summary of QC samples for all PK studies and Study RECOURSE is listed in [Table 29](#). QC samples were prepared in duplicate in each run. Acceptance criteria for QC samples in each run were met (%bias within  $\pm 15\%$  of the nominal concentration for at least 4/6 of QC samples and at least 50% QC samples at each level within 15% of the nominal concentrations, and a minimum of three concentrations of QCs).

**Table 29.** QC Samples for Trifluridine, FTY, and Tipiracil in Plasma – All PK Studies and Study TAS-102-301

Analyte	Clinical Study	Parameter	LQC (10 ng/mL)	MQC (250 ng/mL)	HQC (4000 ng/mL)
FTD	J001-10040010	Concentration (ng/mL)	9.08 - 11.1	242 - 276	3610 - 4140
		Accuracy (%)	90.8 - 111.0	96.8 - 110.4	90.3 - 103.5
	J004-10040040	Concentration (ng/mL)	8.21 - 10.9	242 - 290	3690 - 4270
		Accuracy (%)	82.1 - 109.0	96.8 - 116.0	92.3 - 106.8
	TPU-TAS-102-102	Concentration (ng/mL)	9.29 - 10.8	254 - 270	3820 - 4270
		Accuracy (%)	92.9 - 108.0	101.6 - 108.0	95.5 - 106.8
	TPU-TAS-102-103	Concentration (ng/mL)	8.51 - 10.8	237 - 279	3690 - 4480
		Accuracy (%)	85.1 - 108.0	94.8 - 111.6	92.3 - 112.0
	TPU-TAS-102-104	Concentration (ng/mL)	8.19 - 11	225 - 282	3790 - 4540
		Accuracy (%)	81.9 - 110.0	90.0 - 112.8	94.8 - 113.5
	TPU-TAS-102-301	Concentration (ng/mL)	8.62 - 11.1	251 - 306	3870 - 4550
		Accuracy (%)	86.2 - 111.0	100.4 - 122.4	96.8 - 113.8
Analyte	Clinical Study	Parameter	LQC (10 ng/mL)	MQC (250 ng/mL)	HQC (4000 ng/mL)
FTY	J001-10040010	Concentration (ng/mL)	9.23 - 11.6	252 - 283	3580 - 4200
		Accuracy (%)	92.3 - 116.0	100.8 - 113.2	89.5 - 105.0
	J004-10040040	Concentration (ng/mL)	10.1 - 12.6	249 - 279	3500 - 3970
		Accuracy (%)	101.0 - 126.0	99.6 - 111.6	87.5 - 99.3
	TPU-TAS-102-102	Concentration (ng/mL)	9.4 - 11.2	261 - 287	3780 - 4360
		Accuracy (%)	94.0 - 112.0	104.4 - 114.8	94.5 - 109.0
	TPU-TAS-102-103	Concentration (ng/mL)	7.75 - 11.9	232 - 295	3750 - 4460
		Accuracy (%)	77.5 - 119.0	92.8 - 118.0	93.8 - 111.5

	TPU-TAS-102-104	Concentration (ng/mL)	8.01 - 11.4	241 - 292	3830 - 4540
		Accuracy (%)	80.1 - 114.0	96.4 - 116.8	95.8 - 113.5
<b>Analyte</b>	<b>Clinical Study</b>	<b>Parameter</b>	<b>LQC (0.4 ng/mL)</b>	<b>MQC (10 ng/mL)</b>	<b>HQC (160 ng/mL)</b>
TPI	J001-10040010	Concentration (ng/mL)	0.364 - 0.457	9.89 - 10.6	156 - 168
		Accuracy (%)	91.0 - 114.3	98.9 - 106.0	97.5 - 105.0
	J004-10040040	Concentration (ng/mL)	0.278 - 0.46	9.88 - 11.3	126 - 175
		Accuracy (%)	69.5 - 115.0	98.8 - 113.0	78.8 - 109.4
	TPU-TAS-102-102	Concentration (ng/mL)	0.375 - 0.496	9.77 - 10.4	156 - 167
		Accuracy (%)	93.8 - 124.0	97.7 - 104.0	97.5 - 104.4
	TPU-TAS-102-103	Concentration (ng/mL)	0.355 - 0.453	9.79 - 11.4	155 - 183
		Accuracy (%)	88.8 - 113.3	97.9 - 114.0	96.9 - 114.4
	TPU-TAS-102-104	Concentration (ng/mL)	0.349 - 0.458	9.46 - 10.8	151 - 166
		Accuracy (%)	87.3 - 114.5	94.6 - 108.0	94.4 - 103.8
	TPU-TAS-102-301	Concentration (ng/mL)	0.346 - 0.493	8.83 - 10.6	141 - 170
		Accuracy (%)	86.5 - 123.3	88.3 - 106.0	88.1 - 106.3

Source: Summary of Biopharmaceutics Studies and Associated Analytic Methods, Table 15, Page 44

### 3 DETAILED LABELING RECOMMENDATIONS

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4 APPENDICES

### 4.1 PHARMACOMETRICS REVIEW

## OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

### 1 SUMMARY OF FINDINGS

#### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

##### 1.1.1 What are the findings by population PK analyses to support the dosing of Lonsurf in overall patient population or/and subgroups of patients?

###### ***Body surface area (BSA)***

Clearance of Lonsurf is dependent on BSA based on population PK covariate analysis. This supports the proposed BSA adjusted dosing (35 mg/m<sup>2</sup> BID on Days 1 through 5 and Days 8 through 12 of each 28-day cycle).

###### ***Hepatic Impairment***

The PK of Trifluridine (FTD) and Tipiracil (TPI) have not been studied in patients with moderate to severe hepatic impairment. As a measure of liver function, serum albumin (ALB) was a significant covariate for clearance of FTD based on population PK analysis with patients with normal liver function and mild hepatic impairment. However liver function parameters (e.g., ALP and BIL) were not significant covariates for PK parameters of either FTD or TPI. The results of an *in vitro* study indicated that the plasma protein binding ratio of FTD is more than 96% in human, suggesting the association between ALB and clearance of FTD would be secondary to the plasma protein binding. So the PK of FTD and TPI are expected to be similar in patients with normal hepatic function and mild hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment.

###### ***Renal Impairment***

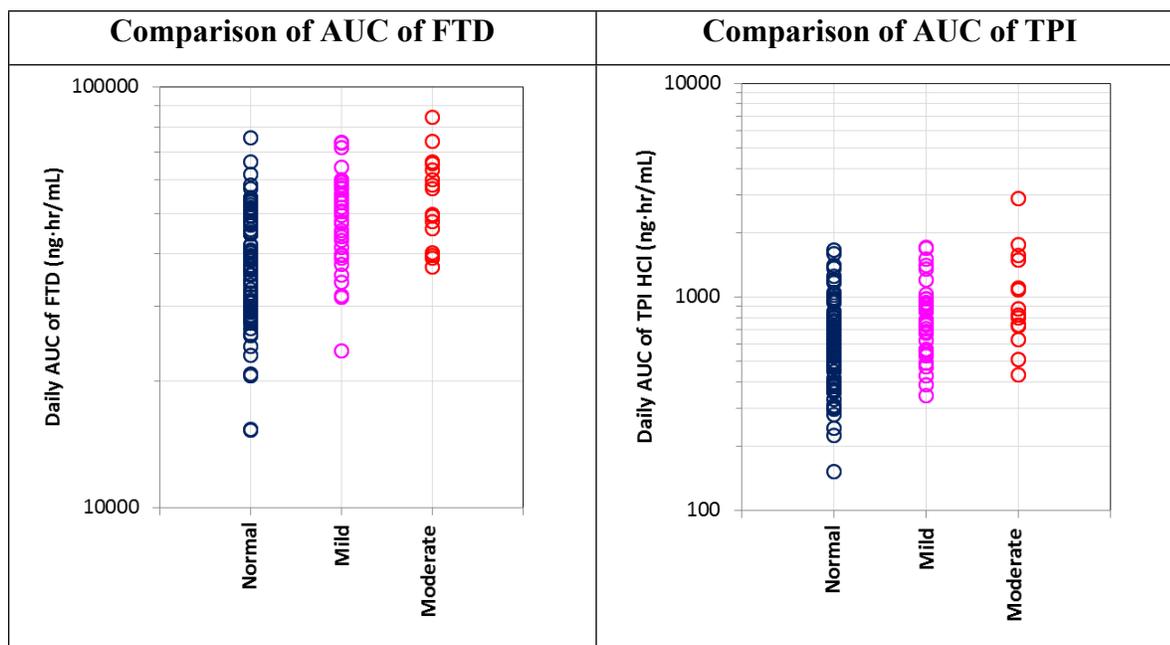
Creatinine clearance (CL<sub>cr</sub>) was a significant covariate for PK of FTD and TPI. However the effect of renal impairment on PK is not clinically important. In phase 3 study TPU-TAS-102-

301, the AUC at steady state of FTD following the proposed dosing was increased by 31% in patients with mild renal impairment (CLcr = 60-89 mL/min, n =38) and 43% in patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 16) as compared to patients with normal renal function (CLcr ≥ 90 mL/min, n=84). The AUC at steady state of TPI following the proposed dosing was increased by 34% in patients with mild renal impairment (CLcr = 60-89 mL/min, n =38) and 65% in patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 16) as compared to patients with normal renal function (CLcr ≥ 90 mL/min, n=84) (Table 30). However, there is substantial overlap in exposure of FTD and TPI among patients with different renal function (Figure 9), so no adjustment on starting dose is warranted for patients with mild and moderate renal impairment (CLcr of 30 to 89 mL/min).

**Other Factors**

Age (33-82 years), sex, race (White or Asian) and concomitant medication with OCT2 inhibitor are not significant covariate for the PK of FTD and TPI.

**Figure 9. Comparison of AUC of FTD and TPI across each renal function group in phase 3 study TPU-TAS-102-301**



Sources: Sponsor’s Analysis of renal function effects on PK from study TPU-TAS-102-30, Page 5 and 7

**Table 30. Summary of AUC for each renal function subgroup**

Renal Impairment Based on CLcr	Analyte PK Parameter Unit Period Method	FTD	TPI HCl
		Daily AUC ng*hr/mL Day 12 Pop-PK	Daily AUC ng*hr/mL Day 12 Pop-PK
Normal (CLcr >=90 mL/min)	n	84	84
	Mean	38812.0	630.7
	SD	10905.3	300.5
	CV	28%	48%
Mild Impairment (CLcr 60-89 mL/min)	n	38	38
	Mean	50177.8	825.9
	SD	11835.6	343.0
	CV	24%	42%
	Ratio of Geometric Mean to the Normal Group Estimate (95% CI)	1.31 (1.17 - 1.46)	1.34 (1.13 - 1.59)
	Moderate Impairment (CLcr 30-59 mL/min)	n	16
Mean	54898.0	1060.9	
SD	13675.8	616.5	
CV	25%	58%	
Ratio of Geometric Mean to the Normal Group Estimate (95% CI)	1.43 (1.22 - 1.68)	1.65 (1.29 - 2.11)	

Sources: Sponsor's Analysis of renal function effects on PK from study TPU-TAS-102-30, Page 8

**1.1.2 What is the characteristic of exposure-response (E-R) relationship for efficacy and safety?**

The E-R relationship for efficacy and safety could not be adequately characterized as only 26% percent (138/534) patients in the Lonsurf treatment arm in phase 3 study (TPU-TAS-102-301) had evaluable PK data.

**1.2 Recommendations**

The Division of Pharmacometrics in Office of Clinical Pharmacology has reviewed the information contained in NDA 207981. This NDA is considered acceptable from a pharmacometrics perspective.

**1.3 Label Statements**

Please refer to Section 3 - Detailed Labeling Recommendations in clinical pharmacology review.

**2 RESULTS OF SPONSOR'S POPULATION PK ANALYSIS**

**2.1 Data and Patients Characteristics**

The PK data of clinical studies listed in Table 31 were combined and used in this population PK analysis.

**Table 31: Summary of studies used for population PK analysis**

Study number	Study objective and design Dose and regimen	Number of planned patients	Number of patients analyzed	Sampling schedule (postdose)
J001-10040010	Phase 1 ascending dose escalation study in Japanese patients 15 to 35 mg/m <sup>2</sup> BID x 5 days a week followed by 2 days rest for 2 weeks every 4 weeks	NA	21	9 points on day 1 and 12 of cycle 1; 0, 15, 30 min, 1, 2, 4, 6, 8, and 10 hr
TPU-TAS-102-301	Multinational double-blind, two-arm, parallel, randomized phase 3 comparison study; RECURSE study 35 mg/m <sup>2</sup> BID x 5 days a week followed by 2 days rest for 2 weeks every 4 weeks	to obtain 100 evaluable	139	3 points on day 12 <sup>a</sup> of cycle 1; 1.0, 3.0, and 6.0 hr
TPU-TAS-102-102	Phase 1, open-label, randomized, parallel group study in USA patients 35 mg/m <sup>2</sup> BID x 5 days a week followed by 2 days rest for 2 weeks every 4 weeks	40	39	12 points on day 1 of cycle 1; 0, 15, 30 min, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr 7 points on day 12 of cycle 1, 2, and 3; 0, 30 min, 1, 2, 4, 8, and 12 hr
TPU-TAS-102-103	Phase 1 study to evaluate the cardiac safety study in USA and UK patients 35 mg/m <sup>2</sup> BID x 5 days a week followed by 2 days rest for 2 weeks every 4 weeks	45	42	10 points on day 1 and 12 of cycle 1; 0, 20, 35 min, 1 hr 5 min, 2 hr 5 min, 4 hr 5 min, 6 hr 5 min, 8 hr 5 min, 10 hr 5 min, and 12 hr 5 min

<sup>a</sup> In study J001-10040010, TPU-TAS-102-102, and TPU-TAS-102-103, the data of only day 12 were used in this analysis. In study TPU-TAS-102-301, the data of Day 9, Day 10 or Day 11 were used in case that blood sampling on Day 12 was not feasible. Pre-dose time point is shown as 0.

Sources: Sponsor's Pharmacokinetic Analysis Report, Page 15

Summary of patient characteristics in the PK datasets was provided in Table 32.

**Table 32: Patient characteristics**

Study		Overall	TPU-TAS-102-301	TPU-TAS-102-102	TPU-TAS102-103	J001-10040010
Actual Dose (mg/body as FTD)	n	239	138	39	41	21
	mean	61	62	64	65	38
	SD	11	7	8	9	12
	CV	17.4%	11.1%	12.0%	13.3%	30.1%
	median	60	60	65	65	40
	max	80	75	80	80	55
	min	15	45	50	50	15
Age (years)	n	239	138	39	41	21
	mean	60	61	57	59	58
	SD	10	10	10	9	7
	CV	16.6%	16.9%	17.5%	15.5%	12.4%
	median	61	62	57	58	59
	max	82	82	76	78	68
	min	33	33	37	39	38
Body Height (cm)	n	238	138	39	40	21
	mean	168	168	170	170	162
	SD	10	9	10	11	10
	CV	5.8%	5.3%	5.8%	6.7%	6.2%
	median	168	168	171	171	163
	max	194	186	194	193	177
	min	142	142	152	150	143
Body Weight (kg)	n	238	138	39	40	21
	mean	73.6	72.6	78.3	80.6	58.0
	SD	17.6	16.0	17.3	19.7	14.1
	CV	23.9%	22.0%	22.1%	24.4%	24.3%
	median	72.0	70.0	78.8	77.0	54.4
	max	123.2	121.1	109.6	123.2	94.9
	min	29.3	42.0	44.5	50.5	29.3
Body Surface Area (m <sup>2</sup> )	n	239	138	39	41	21
	mean	1.82	1.81	1.89	1.91	1.56
	SD	0.24	0.22	0.24	0.26	0.22
	CV	13.4%	11.9%	12.6%	13.8%	14.0%
	median	1.81	1.81	1.86	1.93	1.55
	max	2.48	2.24	2.41	2.48	2.05
	min	1.10	1.28	1.43	1.44	1.10

Study		Overall	TPU-TAS-102-301	TPU-TAS-102-102	TPU-TAS102-103	J001-10040010
Albumin (g/dL)	n	239	138	39	41	21
	mean	3.77	3.78	3.72	3.75	3.85
	SD	0.46	0.48	0.40	0.49	0.35
	CV	12.1%	12.6%	10.8%	13.1%	9.0%
	median	3.90	3.90	3.80	3.80	4.00
	max	4.70	4.70	4.60	4.50	4.30
	min	2.20	2.20	2.70	2.20	2.90
Alkaline Phosphatase (U/L)	n	238	137	39	41	21
	mean	248	256	157	172	518
	SD	270	262	124	166	460
	CV	109.0%	102.4%	79.0%	96.8%	88.7%
	median	143	143	107	110	387
	max	2322	1462	519	865	2322
	min	36	44	36	39	179
Alanine Aminotransferase (U/L)	n	239	138	39	41	21
	mean	27	27	28	27	31
	SD	22	23	17	16	38
	CV	82.2%	83.5%	61.6%	58.9%	125.7%
	median	21	20	25	22	22
	max	182	132	73	80	182
	min	5	5	8	7	7
Aspartate Aminotransferase (U/L)	n	239	138	39	41	21
	mean	33	35	28	32	35
	SD	24	26	14	20	25
	CV	71.3%	76.6%	48.7%	61.8%	70.6%
	median	26	26	23	25	28
	max	197	197	61	84	121
	min	11	12	11	11	13
Blood Urea Nitrogen (mg/dL)	n	217	116	39	41	21
	mean	15.43	15.36	16.26	14.96	15.21
	SD	6.74	6.89	6.61	5.63	8.32
	CV	43.7%	44.9%	40.7%	37.6%	54.7%
	median	14.60	14.00	15.00	15.13	13.00
	max	48.00	48.00	32.00	38.93	48.00
	min	3.64	3.64	5.00	6.00	8.00
Creatinine Clearance (mL/min)	n	238	138	39	40	21
	mean	103	102	108	109	92
	SD	34	32	37	35	31
	CV	32.5%	31.6%	34.6%	32.2%	33.4%
	median	103	104	104	104	86
	max	200	189	200	187	154
	min	35	41	35	41	43

Study		Overall	TPU-TAS-102-301	TPU-TAS-102-102	TPU-TAS102-103	J001-10040010
Gastrectomy	n	239	138	39	41	21
	Unknown	58%	100%	0%	0%	0%
	No	41%	0%	100%	100%	90%
	Yes	1%	0%	0%	0%	10%
Gender	n	239	138	39	41	21
	Female	41%	37%	46%	51%	33%
	Male	59%	63%	54%	49%	67%
Organic Cation Transporter 2 Inhibitor	n	239	138	39	41	21
	No	90%	89%	90%	90%	95%
	Yes	10%	11%	10%	10%	5%
Performance Status	n	239	138	39	41	21
	0	58%	60%	28%	71%	76%
	1	41%	40%	72%	29%	19%
	2	0%	0%	0%	0%	5%
Primary Diagnosis	n	239	138	39	41	21
	Colorectal	89%	100%	69%	73%	86%
	Gastric	1%	0%	0%	0%	10%
	Other	10%	0%	31%	27%	5%
Race	n	239	138	39	41	21
	Caucasian	61%	57%	82%	83%	0%
	Black	3%	1%	5%	7%	0%
	Hispanic and Latino	3%	2%	10%	2%	0%
	Japanese or Asian	26%	28%	3%	5%	100%
	American Indian or Alaska Native	0%	0%	0%	2%	0%
	Unknown	6%	11%	0%	0%	0%
	Thymidine Analogues	n	239	138	39	41
No	100%	100%	100%	100%	100%	

Sources: Sponsor's Pharmacokinetic Analysis Report, Page 25, 26

## 2.2 Results

### 2.2.1 Population PK analysis for FTD

The structural model of PK for FTD is a 1-Compartment model with transit absorption model (nt=4). The estimates of fixed and random effect of final model for FTD were provided in Table 33. The PK data of FTD can be adequately described by the final model (Figure 10). BSA, CLcr and ALB were identified as significant covariates for PK of FTD.

**Table 33: Summary of final model parameter estimated for FTD**

1-Compartment model with transit absorption model (nt=4)

$$Vd/F = 10.0 \times (BSA/1.81)^{0.94} \times \exp(\eta_{i, Vd/F})$$

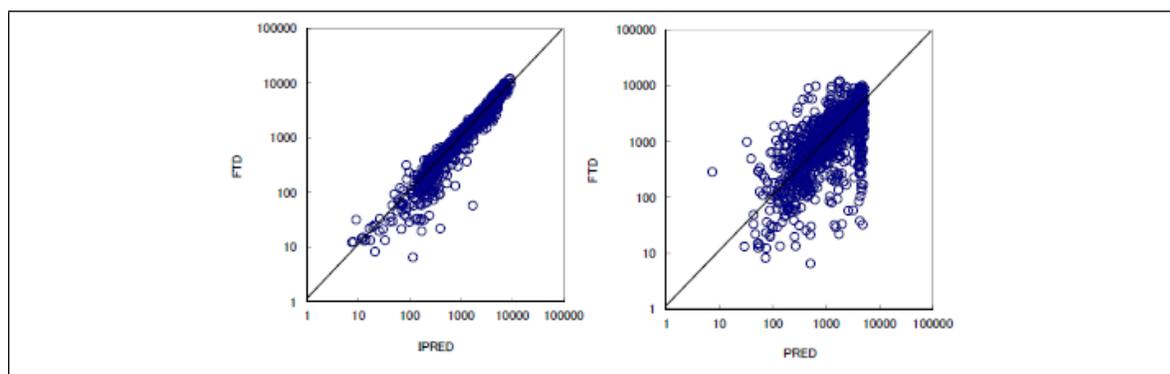
$$CL/F = 2.93 \times (CLCR/103)^{0.507} \times (ALB/3.90)^{-0.633} \times \exp(\eta_{i, CL/F})$$

Run No.	69		
Parameter	Mean	RSE (%)	Shrinkage (%)
Population Mean			
Vd/F (L)	10.0	2.32	NA
CL/F (L/hr)	2.93	2.30	NA
KA (1/hr)	5.43	14.8	NA
MTT (hr)	0.640	7.23	NA
CLCR	0.507	11.8	NA
ALB	-0.633	29.2	NA
BSA	0.940	16.3	NA
Inter-individual Variability			
IIV Vd/F (CV%)	25.3	17.0	26.2
IIV CL/F (CV%)	32.2	13.2	6.41
COV between Vd/F and CL/F	0.0401	27.9	NA
IIV KA (CV%)	NA	NA	NA
IIV MTT (CV%)	92.1	11.3	15.0
Residual Variability			
σ <sub>prop</sub> (%)	21.1	6.45	20.3
σ <sub>add</sub> (ng/mL)	86.3	14.5	

RSE: Relative standard error, σ: Variance of residual error, prop: Proportional residual error model, add: Additive error model, NA: Not applicable, IIV: Inter-individual variability, Vd/F: Apparent distribution volume, CL/F: Apparent oral clearance, KA: Absorption rate constant, MTT: Mean transit time, CLCR: Creatinine clearance, ALB: Albumin, BSA: Body surface area, COV: Covariance, nt: Number of transit compartment, CV: Coefficient of variation, η: Inter-individual residual

Sources: Sponsor's Pharmacokinetic Analysis Report, Page 58

**Figure 10: Diagnostic plots of final model for FTD**



Sources: Sponsor's Pharmacokinetic Analysis Report, Page 61

Reviewer's comments: BSA is not included as covariate for clearance in the final model. It is known that BSA is highly correlated with CLcr since the effect of body size is already captured in the calculation of CLcr. So clearance of FTD is apparently associated with BSA secondary to its association with CLcr. However, including both CLcr and BSA as covariate for clearance reduced the value of objective function by 17.587. Therefore, BSA is a significant covariate for

clearance of FTD after controlling for CLcr, suggesting BSA and clearance is associated independent on CLcr. This serves the basis for the proposed BSA adjusted dosing.

### 2.2.2 Population PK analysis for TPI

The PK of TPI can be described by a 2-Compartment model with transit absorption model (nt=4). The estimates of fixed and random effect of final model for TPI were provided in Table 34. The PK data of TPI can be adequately described by the final model (Figure 11).

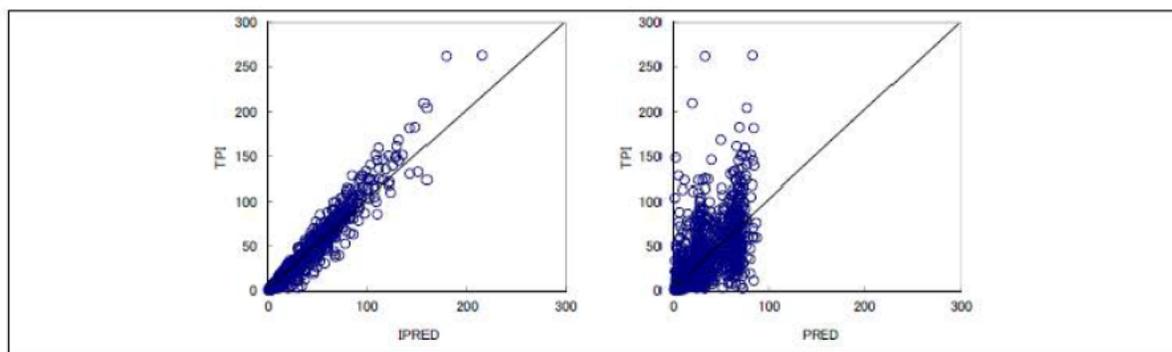
**Table 34: Summary of final model parameter estimated for TPI**

2-Compartment model with transit absorption model (nt=4)			
$Vd/F = 192 \times (BSA/1.81)^{1.46} \times \exp(\eta_{i, VdF})$			
$CL/F = 88.7 \times (CLCR/103)^{0.592} \times \exp(\eta_{i, CLF})$			
Run No.	79		
Parameter	Mean	RSE (%)	Shrinkage (%)
Population Mean			
Vd/F (L)	192	8.49	NA
V2 (L)	240	16.0	NA
CL/F (L/hr)	88.7	2.90	NA
Q (L/hr)	16.0	12.8	NA
KA (/hr)	0.845	8.28	NA
MTT (hr)	0.867	5.85	NA
CLCR	0.592	15.1	NA
BSA	1.46	25.3	NA
Inter-individual Variability			
IIV Vd/F (CV%)	62.7	16.3	21.4
IIV CL/F (CV%)	44.3	14.7	4.58
COV between Vd/F and CL/F	0.137	23.9	NA
IIV KA (CV%)	NA	NA	NA
IIV MTT (CV%)	72.9	12.4	12.2
Residual Variability			
$\sigma_{prop}$ (%)	27.1	4.24	20.3

RSE: Relative standard error,  $\sigma$ : Variance of residual error, NA: Not applicable, IIV: Inter-individual variability, Vd/F: Apparent distribution volume of central compartment, CL/F: Apparent oral clearance, KA: Absorption rate constant, MTT: Mean transit time, CLCR: Creatinine clearance, BSA: Body surface area, COV: Covariance, Q: Clearance between compartments, V2: Apparent distribution volume of peripheral compartment, CV: Coefficient of variation,  $\eta$ : Inter-individual residual, nt: Number of transit compartment, prop: Proportional residual error model

Sources: Sponsor's Pharmacokinetic Analysis Report, Page 96

**Figure 11: Diagnostic plots of final model for TPI**



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/s/  
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XIANHUA W CAO  
08/20/2015

JINGYU YU  
08/20/2015

ANSHU MARATHE  
08/20/2015  
On behalf of Yaning Wang.

HONG ZHAO  
08/20/2015  
I concur.

NAM ATIQUR RAHMAN  
08/21/2015

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA 207981**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA/BLA Number	207981	Brand Name	Lonsurf
OCP Division (I, II, III, IV, V)	OCP Division V	Generic Name	TAS-102
Medical Division	DOP2	Drug Class	anti-neoplastic thymidine-based nucleoside analogue (trifluridine and tipiracil hydrochloride combination with fixed molar ratio of 1:0.5)
OCP Reviewer	Xianhua(Walt) Cao, Ph D.	Indication(s)	metastatic colorectal cancer (CRC)
OCP Team Leader	Hong Zhao Ph.D. (CP); Liang Zhao, Ph.D. (PM)	Dosage Form	Tablets ( 15 and 20 mg)
Pharmacometrics Reviewer	Jerry Yu, Ph.D.	Dosing Regimen	35 mg/m <sup>2</sup> /dose, twice daily (BID) for 5 days a week with 2 days rest for 2 Weeks, followed by a 2 weeks rest, repeated every 4 weeks
Date of Submission	12/19/14	Route of Administration	Orally (b) (4)
Estimated Due Date of OCP Review	10/23/15?	Sponsor	Taiho Oncology, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	12/18/15		

***Clin. Pharm. and Biopharm. Information***

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:	x	1		TPU-TAS-102-108, proposed as PMC, CSR expected 2Q2015
Isozyme characterization:				
Blood/plasma ratio:	x	1		Study 11DA34
Plasma protein binding:	x	2		Studies AE-2350-2G and AE-2350-3G
<b>Pharmacokinetics (e.g., Phase I) -</b>	x			
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 207981

single dose:				
multiple dose:	x	3		Study J001-10040010, TPU-TAS-102-101, TPU-TAS-102-102,
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	2		Study J001-10040010, TPU-TAS-102-101
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	x	1		TPU-TAS-102-102: PK contribution of TPI
In-vivo effects of primary drug:				
In-vitro:	x	15		
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x	1		TPU-TAS-102-107, proposed as PMC, study initiated 4Q2014
hepatic impairment:	x	1		TPU-TAS-102-106, proposed as PMC, study initiated 4Q2014
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	x	1		TPU-TAS-102-103: cardiac safety
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:	x	3		J001-10040010; TPU-TAS-102-102; TPU-TAS-102-103
Data sparse:	x	1		TPU-TAS-102-301
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:	x	1		Study TPU-TAS-102-104
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>	x	1		Study J004-10040040
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		25		

On **initial** review of the NDA/BLA application for filing:

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA 207981\_ Ionsurf

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA 207981**

<b>Criteria for Refusal to File (RTF):</b> This OCP checklist applies to NDA, BLA submissions and their supplements					
<b>No</b>	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	The to-be-marketed formulation tablets are identical to the Late Clinical Trial Material (CTM) Formulation, which was used in the pivotal study TPU-TAS-102-301
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
<b>Complete Application</b>					

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA 207981**

10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			
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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA 207981**

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Sponsor proposed as PMC.
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		Sponsor proposed as PMC.
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Waivered from pediatric study requirements
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Waivered from pediatric study requirements
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			ER analysis is proposed as PMC.
<b>General</b>					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA 207981**

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Xianhua (Walt) Cao Ph.D.	January 28, 2015
Reviewing Clinical Pharmacologist	Date
Hong Zhao Ph.D.	January 28, 2015
Team Leader/Supervisor	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XIANHUA W CAO  
02/24/2015

HONG ZHAO  
02/24/2015  
I concur.