CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 9-29-2015

From: Leyla Sahin, MD
Medical Officer,
Division of Pediatric and Maternal Health, Maternal Health Team

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Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, MD
Director,
Division of Pediatric and Maternal Health

To: Division of Oncology Products 2

Drugs: Lonsurf (trifluridine/tipiracil hydrochloride) tablets; NDA 207981

Proposed Indication: Metastatic colorectal cancer who have been previously treated with, (b) (4) (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

Subject: Pregnancy and Lactation Labeling

Applicant: Taiho Oncology, Inc.

Materials Reviewed: • Applicant's proposed labeling

Consult Question: Please assist with Pregnancy and Lactation Labeling

INTRODUCTION

The applicant submitted a new molecular entity (NME) combination original new drug application (NDA) for Lonsurf (trifluridine/tipiracil hydrochloride) on December 19, 2014 (see description of trifluridine and tipiracil below, under "Product Background". The proposed indication for Lonsurf is the treatment of patients with metastatic colorectal cancer 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 Division of Oncology Products 2 (DOP 2) consulted the Division of Pediatric and Maternal Health (DPMH) on February 26, 2015, to assist with reviewing the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling.

BACKGROUND

Product Background

Trifluridine is an antineoplastic thymidine-based nucleoside analogue and tipiracil hydrochloride is a thymidine phosphorylase inhibitor. Trifluridine was approved in 1980 as an ophthalmic solution for topical treatment of keratoconjunctivitis due to herpes simplex virus, types 1 and 2.

Inclusion of tipiracil in Lonsurf increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase. Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation.

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR).[1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015. The recommendations in this review are consistent with the PLLR format.

DISCUSSION

A search of published literature was performed and no reports on the safety of trifluridine or tipiracil in pregnancy or lactation were found.

The applicant's proposed labeling included contraception recommendations for (b) (4) months after treatment, without inclusion of a scientific rationale for the duration of contraception use. The

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

half-life of trifluridine is 2.1 hours and that of tipiracil is 2.4 hours. The drug is administered orally twice a day. Based on six half-lives, trifluridine and tipiracil should be cleared in 18 hours; therefore, contraception is not needed after treatment.

Regarding lactation, DPMH and DOP2 discussed that trifluridine and tipiracil should be cleared in 18 hours. There was agreement to include a recommendation to not breastfeed for a day following the last dose, in order to allow sufficient time for the drug to clear.

Nonclinical studies showed that trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice. Based on these findings, DPMH and DOP2 agreed to include a recommendation for males with female partners of reproductive potential to use condoms during treatment with Lonsurf and for at least three months after the final dose. Three months is the duration of one spermatogenesis cycle, and is consistent with the Office of Hematology and Oncology Products' recommendation for duration of contraception for drugs with a short half-life.

CONCLUSION
The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR.

DPMH LABELING RECOMMENDATIONS
DPMH discussed our labeling recommendations with DOP 2 at a meeting on August 18, 2015. DPMH recommendations are below and reflect the discussions with DOP 2 at that meeting.
See final labeling for all of the labeling revisions negotiated with the applicant.

5. WARNINGS AND PRECAUTIONS

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m^2 twice daily.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LONSURF can cause fetal harm (b) (4) . LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans *[see Data]*. There are no available data on

LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m^2 twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine, tipiracil, and/or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ^{14}C-FTD or ^{14}C-tipiracil (TPI). Levels of FTD derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifuridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman *[*see *Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[*see *Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

(b) (4)

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose *[*see *Use in Specific Populations (8.2)]*.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEYLA SAHIN
09/29/2015

TAMARA N JOHNSON
09/29/2015

LYNNE P YAO
09/29/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA Product Name: 207-981, Lonsurf ((trifluridine and tipiracil hydrochloride)

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Trial

2963-1

PMR/PMC Schedule Milestones:

Final Protocol Submission:	Submitted
Study/Trial Completion:	9/30/ 2017
Final Report Submission:	12/31 2017
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical pharmacokinetic trial is to determine appropriate Lonsurf dose in patients with moderate or severe hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☒ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for NDAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 207-981, Lonsurf (trifluridine and tipiracil hydrochloride)
Product Name:

PMR/PMC Description: Renal Impairment Pharmacokinetic Trial

2963-2

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	Submitted
	Study/Trial Completion:	9/30/2017
	Final Report Submission:	12/31/2017
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

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 would be expected to 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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical pharmacokinetic trial is to determine an appropriate Lonsurf dose in patients with severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
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- ☒ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for NDAs)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIANHUA W CAO
09/22/2015

HONG ZHAO
09/22/2015
I concur.

JEFFERY L SUMMERS
09/22/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 207981

Application Type: New NDA

Name of Drug/Dosage Form: Lonsurf (trifluridine/tipiracil), 15 mg and 20 mg tablets

Applicant: Taiho Oncology, Inc.

Receipt Date: December 19, 2014

Goal Date: December 19, 2015

1. Regulatory History and Applicant's Main Proposals

This New Drug Application (NDA) is for full approval of Lonsurf [Proposed] (trifluridine/tipiracil) for the "treatment of patients with metastatic colorectal cancer 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 NDA will be supported by efficacy and safety data from the following pivotal study based on overall survival (OS) results:

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

The NDA will also include the efficacy and safety data from the following supportive studies:

- Study J003-10040030: entitled "Placebo-Controlled, Multicenter, Double-Blind, Randomized, Phase II Study of TAS-102 in Patients with Unresectable Advanced or Recurrent Colorectal Cancer Who Have Had 2 or More Chemotherapy Regimens and Who Are Refractory or Intolerant to Fluoropyrimidine, Irinotecan, and Oxaliplatin."

- Study J001-10040010 entitled, "TAS-102 Phase I Clinical Study in Patients with Solid Tumors."

- Study J004-10040040 entitled, "Clinical Pharmacology Study of Food Effect on TAS-102."

- Study TPU-TAS-102-101 entitled, "A Phase 1, Open-label, Non-randomised, Dose finding, Safety and Tolerability Study of Orally Administered TAS-102 in Patients with Refractory Metastatic Colorectal Cancer."

- Study TPU-TAS-102-102 entitled, "A Phase 1, open-label, randomised, parallel group study evaluating the pharmacokinetics of trifluridine (FTD) as a component of TAS-102 compared with FTD alone."

- Study TPU-TAS-102-103 entitled, "A Phase 1 study to evaluate the cardiac safety of orally administered TAS-102 in patients with advanced solid tumours."

- Study TPU-TAS-102-104 entitled, "A Phase 1, open-label, randomised, crossover study evaluating the bioavailability of TAS-102 tablets relative to an oral solution containing equivalent amounts of trifluridine (FTD) and tipiracil hydrochloride (TPI)."

Regulatory History:
On March 24, 2014, Oncology, Inc. (Taiho) received approval in Japan for Lonsurf [Proposed] (trifluridine/tipiracil) for the treatment of patients with unresectable advanced or recurrent colorectal cancer (mCRC). This approval was based on the results of the randomized (2:1), double-blind placebo controlled clinical trial conducted in Japan (J003-10040030). The primary endpoint of the trial was overall survival and the primary endpoint was tested with a one-sided alpha of 0.10. Data from this study is proposed for supportive data for the US NDA application.

The regulatory history in the US includes the following: initial development program for the trifluridine/tipiracil began in 1998 in solid tumors; development was suspended in 2009 and reinitiated in 2011; an EOP2 CMC only meeting was held on November 29, 2011; an EOP2 multidiscipline meeting was held December 12, 2011, regarding the data from studies conducted in Japan and seeking feedback on the proposed clinical development plan for treatment of colorectal cancer; new registrational Protocol TPU-TAS-102-301 (RECOURSE) submitted on May 24, 2012; a Pre-NDA CMC only meeting scheduled for December 5, 2013, but cancelled by the sponsor as the information in the preliminary document was sufficient, and a Pre-NDA multidiscipline meeting was held July 31, 2014, to discuss the content and format of the NDA and obtain agreement on any late components of an application.

Finally, Taiho was granted Fast Track Designation for patients with metastatic colorectal cancer who have been previously treated with, [redacted] (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy to demonstrate an improvement in overall survival on September 12, 2014.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

In addition, the following labeling issues were identified:

1. (3)Horizontal line exists between HL and TOC,but only a partial horizontal line exists l

2. (5) Sponsor inserted a space between HL Heading and HL Limitation Statement.

3. (9)Statement is acccurate; however, the drug product does not appear in UPPER CASE.

4. (22) Sponsor has not inserted the Manufacturer name into the statement nor their phone

5. (30)Section 5.1 [redacted] (b) (4) is not present in the TOC

6. (33)Cross-reference under 8.1 is not italicized.

7. (39)Statement is not verbatim. Sponsor will need to update the label to reflect this verbatim

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *No comments.*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Waiver requested was not present in the initial application. If HL extend beyond the*

Selected Requirements of Prescribing Information

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Horizontal line exists between HL and TOC,but only a partial horizontal line exists i*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *No comments.*

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Sponsor inserted a space between HL Heading and HL Limitation Statement.*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *No comments.*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Selected Requirements of Prescribing Information

Comment: *Boxed Warning is not present in the sponosr submitted labeling. Additionally, i*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment: *No comments.*

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Statement is acccurate; however, the drug product does not appear in UPPER*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment: *Statement is acccurate in bold; however, the drug product does not appear in*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *No comments.*

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *Not present in the sponosr submitted labeling*

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment: *Not present in the sponosr submitted labeling*

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: *Not present in the sponosr submitted labeling*

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment: *Not present in the sponosr submitted labeling*

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *Not present in the sponosr submitted labeling as this is a NME*

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *Not present in the sponosr submitted labeling as this is a NME*

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *Not present in the sponosr submitted labeling as this is a NME*

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *Product is "combination of an antineoplastic thymidine-based nucleoside analogue (*

APPEARS THIS WAY ON ORIGINAL

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form (Tablets) noted in the proposed labeling.*

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *FPI only notes hypersensitivity; noted in the HL.*

Adverse Reactions in Highlights

NO 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *Sponsor has not inserted the Manufacturer name into the statement nor their phone*

APPEARS THIS WAY ON ORIGINAL

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *Sponosr submitted labeling noting the verbatim statement in the second bullet above.*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *Sponosr has place holder for month in the above format*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment: *No comments.*

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment: *No comments.*

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *Not present in the sponosr submitted labeling*

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *No comments.*

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *No comments.*

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *Section 5.1 "Bone Marrow Suppression" is not present in the TOC*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *No comments.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *No comments.*

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment: *Cross-reference under 8.1 is not italicized.*

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *Not present in the sponosr submitted labeling as this is a NME*

Selected Requirements of Prescribing Information

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment: *No comments.*

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment: *Not present in the sponosr submitted labeling*

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment: *Not present in the sponosr submitted labeling*

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment: *Hypersensitivity noted under Section 4*

ADVERSE REACTIONS Section in the FPI

NO 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Statement is not verbatim. Sponsor will need to update the label to reflect this* 1

APPEARS THIS WAY ON ORIGINAL

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *Not present in the sponosr submitted labeling as this is a NME*

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *References patient information*

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *Currently not included as a subsection under section 17. Patient Information is in a separate document. Remind the sponsor that once approved must appear at the end of the PI.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GINA M DAVIS
09/16/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 10, 2015
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 207981
Product Name and Strength:	Lonsurf (trifluridine and tipiracil) Tablets, 15 mg/6.14 mg and 20 mg/8.19 mg
Submission Date:	September 8, 2015
Applicant/Sponsor Name:	Taiho Oncology, Inc.
OSE RCM #:	2014-2488
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Lonsurf (Appendix A) to determine they are acceptable from a medication errors perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication errors perspective.

[1] Townsend, O. Label and Labeling Review for Lonsurf (NDA 207981). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JUN 14. 14 p. OSE RCM No.: 2014-2488-1.

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

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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.

/s/

OTTO L TOWNSEND
09/10/2015

CHI-MING TU
09/10/2015

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	57,674
Generic Name	TAS-102
Sponsor	Taiho Oncology, Inc.
Indication	Treatment of advanced solid tumor
Dosage Form	Tablets
Drug Class	Antineoplastic nucleoside analog and thymidine phosphorylase inhibitor
Therapeutic Dosing Regimen	35 mg/m^2 b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not determined
Submission Number and Date	SDN 340/ August 13, 2014
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study was conducted in 2 parts: Cardiac Safety Evaluation (Cycle 1) and Extension (Cycles ≥2) on cardiac repolarization after a single dose and after multiple dose administration. No large change (i.e., > 20 ms) in the QTc interval was detected when TAS-102 was administered 35 mg/m^2. The sponsor did not include positive control (moxifloxacin) arms in this study.

This was non- randomized open-label except for one day of placebo treatment (Day -1) before the start of the TAS-102 dosing study, 44 patients enrolled in the study. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for TAS-102 35 mg/m^2 (FDA Analysis)

Day/Cycle	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Day 1 Cycle 1	12	4.1	(-0.9, 9.1)
Day 12 Cycle 1	12	5.1	(-1.6, 11.9)

The studied dose is the same as proposed therapeutic dose. Observed exposures are similar to those previously reported. Severe renal impairment is estimated to result in doubling or tripling exposure. Hematologic toxicities prevent use of higher doses that studied.

1.2 QT Interdisciplinary Review team's Comments

QT-IRT had previously reviewed the protocol for this study report (12/05/2012). Instead of a dedicated QT study, we had encouraged the Sponsor to incorporate an ECG sub-study into one of the efficacy trials. However, based on the results from this study, we consider that TAS-102 is unlikely to cause clinically relevant QT prolongation and no additional sub-study is needed.

2 BACKGROUND

2.1 Product Information

TAS-102 is a combination of 1M α,α,α-trifluorothymidine (FTD) and 0.5 M 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4(1H,3H)-pyrimidinedione hydrochloride (thymidine phosphorylase inhibitor [TPI]) being developed to treat advanced solid tumors.

2.2 Market approval status

TAS-102 was approved for marketing in Japan in May 2014.

2.3 Preclinical Information

FTD and TPI had no effect on hERG at concentrations of 3, 30 and 300 μM and 1, 10 and 100 μM, respectively. No blood pressure, heart rate, PR, QRS or QT effects were observed in conscious monkeys (see Appendix 5.1).

2.4 Previous Clinical Experience

Adverse events clearly associated with proarrhythmia have not been observed in humans (see Appendix 5.1).

2.5 Clinical Pharmacology

Appendix 5.1 summarizes the key features of TAS-102's clinical pharmacology.

3 SPONSOR'S SUBMISSION

3.1 Overview

The QT-IRT reviewed the protocol prior to conducting this study under IND 57,674. The sponsor submitted the study report TPU-TAS-102-103 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

3.2 TQT Study

3.2.1 Title

A Phase 1 study to evaluate the cardiac safety of orally administered TAS-102 in patients with advanced solid tumors

3.2.2 Protocol Number

TPU-TAS-102-103

3.2.3 Study Dates

First patient dosed: 30 May 2013
Last patient first dose: 11 December 2013
Date cut-off date: 09 January 2014

3.2.4 Objectives

Cardiac Safety Evaluation (Cycle 1):

- To investigate the effect of TAS-102 on cardiac repolarization after a single dose and after multiple dose administration.
- To evaluate the cardiac safety profile of TAS-102.
- To evaluate the relationship between TAS-102 pharmacokinetic and its effect on cardiac repolarization (pharmacokinetics [PK]/ pharmacodynamic analysis).

Extension (Cycles ≥2):

- To assess the safety profile of TAS-102.
- To assess the anti-tumors activity of TAS-102.

3.2.5 Study Description

3.2.5.1 Design

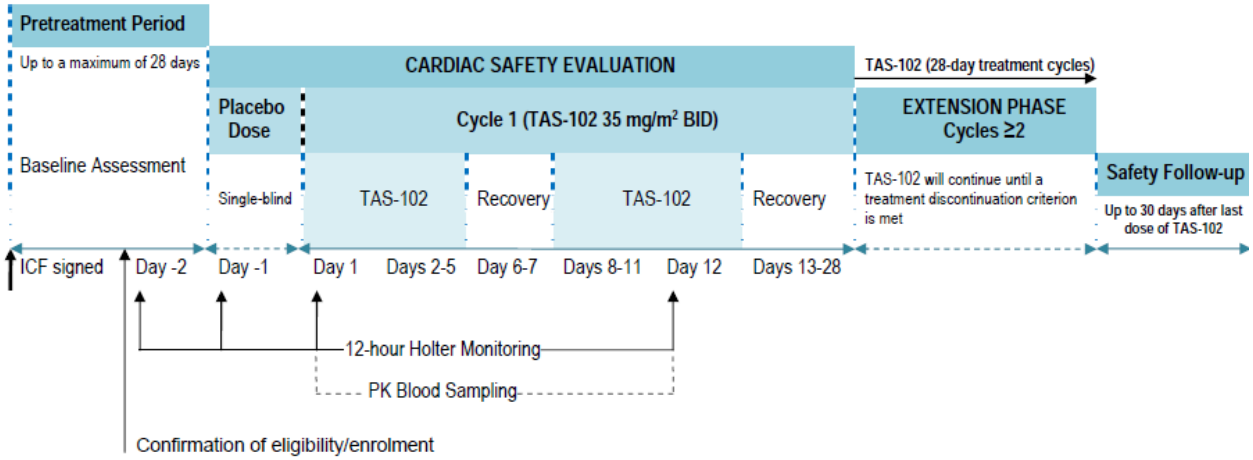
This was a Phase 1, non- randomized study, which was open-label except for one day of placebo treatment (Day -1) before the start of the TAS-102 dosing. The study was conducted in 2 parts: Cardiac Safety Evaluation (Cycle 1) and Extension (Cycles ≥2).

Cardiac Safety Evaluation (Cycle 1):
Prior to the start of TAS-102 dosing, on Day -1 in the morning, all patients received a single, single-blind (patient-blinded) dose of placebo corresponding to a 35 mg/m^2 dose of TAS-102 based on body surface area (BSA). On Day 1 of Cycle 1, all patients received a single dose of TAS-102 35 mg/m^2 in the morning and another dose 12 hours later (after collection of 12-hour PK sample). Afterwards, TAS-102 was administered orally at a dose of 35 mg/m^2 twice daily (BID) on Days 2 through 5. This was followed by a recovery period from Day 6 through Day 7. TAS-102 was again administered orally BID on Days 8 through 12. On Day 12 of Cycle 1, patients received the evening dose of TAS-102 after collection of the 12-hour PK sample. This was followed by a recovery period from Day 13 through Day 28. All doses of TAS-102 or placebo were administered within 1 hour after completing a meal.

Extension (Cycles ≥2):
Patients completing the cardiac safety evaluation (Cycle 1) were eligible to immediately enter the Extension. All patients received TAS-102 35 mg/m^2/dose administered BID, after the morning and the evening meal, for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle). This treatment cycle was repeated every 4 weeks until the patient met any of the treatment discontinuation criteria.

Table 2 presented the overall study design of these 2 parts.

Table 2: Sponsor's Overall Study Design



3.2.5.2 Controls

The Sponsor used a negative (placebo) control.

3.2.5.3 Blinding

This was an open-label study, except for one day (Day-1) during which all patients received a single, single-blind (patient-blinded) oral dose of placebo.

3.2.6 Treatment Regimen

3.2.6.1 Treatment Arms

There are two treatments in this study:

- Placebo
- TAS-102 35 mg/m^2 b.i.d. on Days 2 through 5 and 8 through 12

3.2.6.2 Sponsor's Justification for Doses

In Study TAS-102-101, the tolerability of the 35 mg/m^2/dose BID regimen of TAS-102 (70 mg/m^2/day for 5 days, with 2 days rest, for 2 weeks followed by 2 weeks rest) was confirmed in western patients with refractory colorectal cancer. In addition, the safety profile observed with TAS-102 in Study TAS-102-101 is consistent with that seen at the same dose in the Japanese Phase 2 trial. Therefore, this dose is the recommended Phase 3 dose for further evaluation in a prospective, comparative global study of TAS-102 in refractory colorectal cancer.

As the recommended Phase 3 dose of TAS-102, the regimen of 35 mg/m2/dose BID was selected for evaluation in the present study.

Reviewer's Comment: Applicants dose proposal was reviewed QT review team under IND 57674 on 12/05/2012. This reviewer agrees with the initial assessment.

3.2.6.3 Instructions with Regard to Meals

TAS-102 (or placebo) should be taken with water (240 mL) within 1 hour after completing a meal (morning and evening meal), including on days when Holter monitoring is performed (ie, Day -1, Day 1 of Cycle 1 and Day 12 of Cycle 1).

Reviewer's Comment: The C_{max} of FTD and TPI in the fasted state is 2-fold that of the fed state and therefore represents the high clinical exposure scenario. If TAS-102 is to be administered with food in the clinical studies, dosing with food is acceptable.

3.2.6.4 ECG and PK Assessments

PK and ECG The sampling schedule is tabulated in Table 3.

Table 3. Table of ECG and PK Assessments

Cycle 1 Day 1 and Day 12 (Cardiac Safety Evaluation)		
Sample Collection Type	**Time Points for Extraction of ECG Data During 12-hour Holter Monitoring**	**Time Points for PK Sample Collection[a]**
4 mL blood sample in sodium heparin tube	0 hr (–5 min)	0 min (immediately before dosing)
	TAS-102 Dosing	TAS-102 Dosing
	15 min	20 min
	30 min	35 min
	1.0 hr	1 hr 5 min
	2.0 hr	2 hr 5 min
	4.0 hr	4 hr 5 min
	6.0 hr	6 hr 5 min
	8.0 hr	8 hr 5 min
	10.0 hr	10 hr 5 min
	12.0 hr	12 hr 5 min

[a] To avoid interference, PK sample collection occurred at least 5 min after the time point for extraction of ECG data.
hr = hours; min=minutes

Reviewer's Comment: The sampling schedule is appropriate.

3.2.6.5 Baseline

The Sponsor used time-matched baseline QTc values on Day -2 for each treatment as baseline values.

3.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

3.2.8 Sponsor's Results

3.2.8.1 Study Subjects

A total of 66 patient signed informed consent, of which 22 failed to meet eligibility criteria. Thus, 44 patients were enrolled in the study. Of the 44 patients in the Safety population, 22 (50%) were male and 22 (50%) were female; the mean age was 59.0 years, and all but 6 patients were white. Most patients (72.7%) had colon cancer and 59.1% of patients had received ≥4 prior chemotherapy regimens (including adjuvant therapies). The demographic and baseline characteristics for the subset of patients in the Cardiac Safety population were similar to those observed for patients in the Safety population.

3.2.8.2 Statistical Analyses

3.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean difference between TAS-102 35 mg/m^2 b.i.d and placebo in ΔQTcI. The sponsor used a repeated measure analysis of variance (ANOVA) models include treatment, time, and treatment by time interaction. Following single- and multiple-dose TAS-102 administration of Cycle 1, the upper bounds of the 1-sided 95% CIs for the differences between TAS-102 and placebo did not exceed 20 ms at any time point on both Days 1 and 12.

Table 4: Sponsor's Result of ΔΔQTcI for TAS-102

Day	Postdose Hour	TAS-102		Placebo		TAS-102 vs Placebo	
		N	LS Means[a]	N	LS Means[a]	Difference	90% CI
Cycle 1 Day 1	0	2	-1.9	2	-0.3	-1.6	(-5.6, 2.4)
	0.25	2	-0.9	2	-1.6	0.7	(-3.3, 4.7)
	0.5	2	-1.3	2	-4.0	2.7	(-1.2, 6.6)
	1	2	-2.0	2	-2.2	0.2	(-3.7, 4.1)
	2	2	-0.9	3	-0.6	-0.3	(-4.2, 3.6)
	4	3	2.2	2	-1.9	4.1	(0.2, 8.1)
	6	2	-3.4	2	-2.6	-0.8	(-4.8, 3.1)
	8	2	-1.5	2	-3.3	1.8	(-2.3, 5.9)
	10	2	-1.3	2	-3.5	2.2	(-1.7, 6.2)
	12	2	-0.1	1	-4.9	4.8	(-0.3, 9.8)
Cycle 1 Day 12	0	2	-0.9	2	-0.4	-0.5	(-5.6, 4.5)
	0.25	2	-1.3	2	-1.6	0.3	(-4.6, 5.2)
	0.5	2	-1.8	2	-3.6	1.8	(-3.1, 6.7)
	1	2	-3.3	2	-2.1	-1.1	(-6.0, 3.7)
	2	2	-2.1	3	-0.6	-1.5	(-6.3, 3.4)
	4	2	-0.4	2	-1.4	1.0	(-3.9, 5.9)
	6	3	-3.4	2	-2.5	-1.0	(-5.7, 3.8)
	8	2	0.3	2	-3.3	3.6	(-1.5, 8.7)
	10	2	-3.9	2	-3.3	-0.7	(-5.7, 4.3)
	12	1	0.2	1	-3.7	3.9	(-2.5, 10.3)

[a] Repeated measures ANOVA model: change from baseline in QTcI result = TREATMENT + TIME + TREATMENT * TIME. Compound symmetry covariance was used. Measurements at different time points within each patient's treatment were treated as repeated measures.
Source: Clinical Study Report, Section 11.1.2.1, Table 14, Page 64/741

Reviewer's Comments: We will provide our independent analysis results in Section 5.2. Our results are similar to sponsor's findings.

3.2.8.2.2 Assay Sensitivity

No assay sensitivity established because no positive control arm included in the study.

3.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. One subject's absolute QTc >500 ms and ΔQTc >60 ms.

3.2.8.3 Safety Analysis

Table 5 lists all serious adverse events in the safety population. One subjects died due to disease progression. Patient 303-006 was a 63-year-old male who withdrew consent for study treatment in Cycle 1. The patient died on Day 35 (26 days after dosing).

Table 5. Listing of Serious Adverse Events (Safety Population)

Patient Number	Preferred Term [CTC Grade[a]]	Day of Onset[b]	Action Taken with Study Medication	Relationship	Reason Categorized as Serious
301-003	Small Intestinal Obstruction [3]	37	Drug interrupted	Not related	Hospitalisation
301-007	Anaemia [4]	29	Dose not changed	Not related	Hospitalisation
	Gastric Ulcer [2]	30	Dose not changed	Not related	Hospitalisation
301-011	Neutropenia [3]	49	Dose reduced	Related	Hospitalisation
	Pyrexia [2]	50	Dose not changed	Not related	Hospitalisation
301-012	Atrial fibrillation [3]	91	Dose not changed	Not related	Hospitalisation
302-006	Abdominal pain [2]	41	Dose not changed	Related	Hospitalisation
	Diarrhoea [2]	41	Does not changed	Related	Hospitalisation
	Chest pain [2]	41	Dose not changed	Not related	Hospitalisation
	Colitis [2]	44	Dose not changed	Related	Hospitalisation
302-012	Bacteraemia [3]	16	Drug interrupted	Not related	Hospitalisation
303-002	Febrile neutropenia [1][c]	117	Dose not changed	Related	Hospitalisation
303-005	Anaemia [2]	132	Dose not changed	Related	Hospitalisation
303-006	Upper gastrointestinal haemorrhage [2]	13	Dose not changed	Not related	Hospitalisation
304-005	Intestinal obstruction [1]	94	Dose not changed	Not related	Hospitalisation
	Abdominal pain lower [3]	121	Dose not changed	Not related	Hospitalisation
	Abdominal pain lower [3]	131	Drug interrupted	Not related	Hospitalisation
	Pelvic pain [3]	131	Drug interrupted	Not related	Hospitalisation
304-008	Pyrexia [3]	29	Drug interrupted	Not related	Hospitalisation
304-011	Pyrexia [1]	77	Dose not changed	Not related	Hospitalisation
	Pyrexia [1]	85	Dose interrupted	Not related	Hospitalisation
	Pyrexia [3]	114	Drug withdrawn	Not related	Hospitalisation
304-014	Ascites [3]	62	Dose not changed	Not related	Hospitalisation

Source: adapted form applicant's report, table 30.

3.2.8.4 Clinical Pharmacology

3.2.8.4.1 Pharmacokinetic Analysis

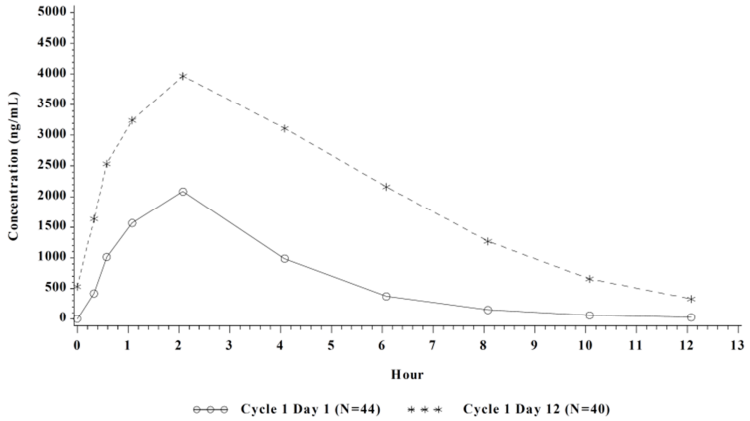
The PK results are presented in Table 6. C_{max} and AUC values in the QT study were similar to exposures expected at the intended clinical dose (same as studied). Concentration time profiles for the three analyses are shown in Figure 1.

Table 6: Descriptive Statistics for Plasma PK Parameters after TAS-102 Dosing on Day 1 and Day 12 of Cycle 1

	FTD		TPI		FTY	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
C_{max} (ng/mL)						
N	44	40	44	40	44	40
Mean	2865.23	5447.75	83.20	78.51	904.05	717.80
SD	1275.13	2693.94	34.19	28.07	286.95	184.38
$AUC_{0\text{-}inf}$ (ng*hr/mL)						
N	44	40	44	39[a]	44	16[b]
Mean	8019.10	25973.32	391.98	410.38	3809.38	4902.57
SD	2607.59	10126.96	179.16	136.20	1112.64	1254.24

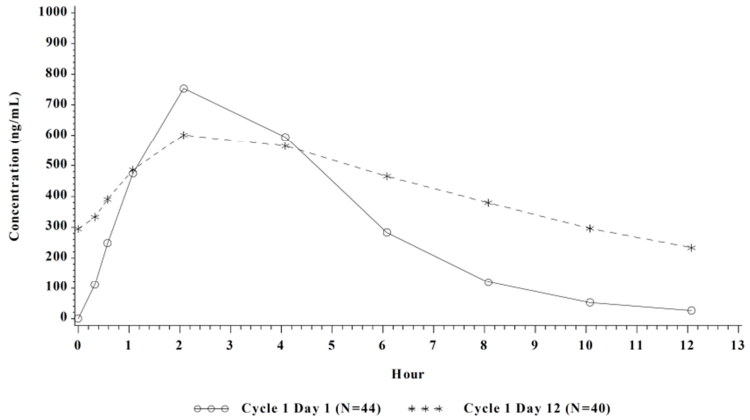
Source: adapted form applicant's report, table 19.

Figure 1. Mean Plasma Concentration Time Profiles after TAS-102 Dosing: FTD



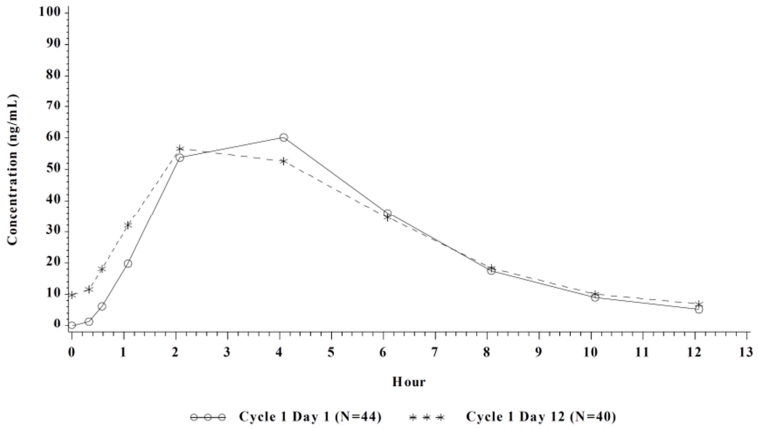
Source: Applicants rapport figure 5:

Mean Plasma Concentration Time Profiles after TAS-102 Dosing: FTY



Source: Applicants rapport figure 6:

Mean Plasma Concentration Time Profiles after TAS-102 Dosing: TPI



Source: Applicants rapport figure 7:

3.2.8.4.2 Exposure-Response Analysis

The relationship of the placebo-adjusted change from baseline in QTc intervals versus plasma TAS-102 concentration was assessed by a linear mixed effect model with the individual QTc change from time-matched placebo (Δ Δ QTc) as the response variable and with treatment group and time point as factors, corresponding log plasma concentration as a covariate, and patient as a random variable

The sponsor estimated positive, statistically significant ($p<0.05$) slopes for TPI and FTD exposure response analysis. A no significant positive slope for FTY exposure QTcI relationship was estimated. None of the 90% confidence interval s at Cmax exceeded the 20 ms threshold.

Reviewer's Analysis: Sponsor's analysis included time as a factor and concentration as a covariate. This approach differs from what is proposed. A standard exposure analysis is presented below. A plot of ΔΔQTcI vs. drug concentrations is presented in Figure 5.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

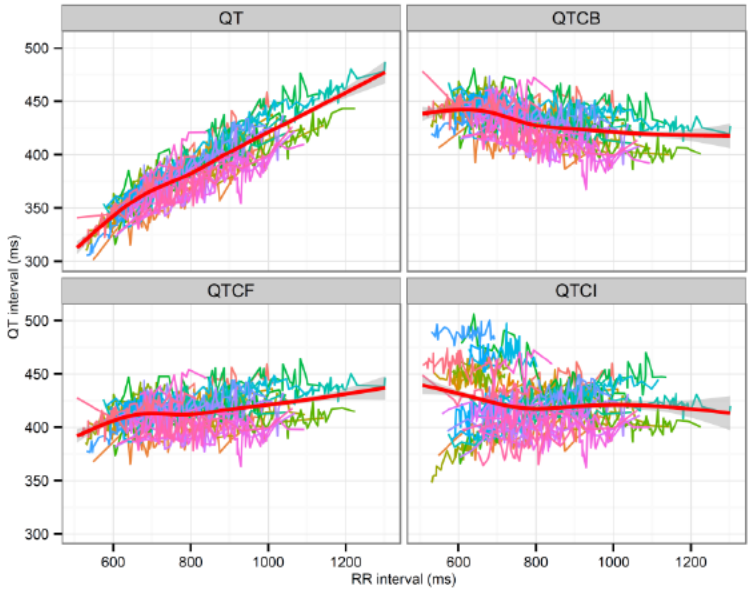
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it appears that QTcI is better than QTcB and QTcF. To be consistent with the sponsor's analyses, this reviewer used QTcI for the primary statistical analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
TAS102 35 MG/M2	42	0.0125	42	0.0110	42	0.0080

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



4.2 Statistical Assessments

4.2.1 QTc Analysis

4.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences between TAS-102 35 mg/m^2 b.i.d. and placebo are 9.1 ms and 11.9 ms on Day 1 Cycle 1 and Day 12 Cycle 1, respectively.

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for TAS-102 35 mg/m^2 b.i.d. on Day 1 Cycle 1 and Day 12 Cycle 1

			Treatment Group			
			TAS102 35 MG/M2			
		ΔQTcI	ΔQTcI		ΔΔQTcI	
Cycle/Day	Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
DAY 1 OF CYCLE 1	0.25	-1.3	39	-0.6	0.7	(-3.5, 4.8)
	0.5	-3.6	39	-1.3	2.3	(-1.2, 5.8)
	1	-0.6	40	-2.1	-1.4	(-4.5, 1.7)
	2	-0.5	37	-2.8	-2.2	(-6.5, 2.0)
	4	-2.8	39	1.5	4.2	(0.1, 8.3)
	6	-2.7	36	-3.6	-0.9	(-4.7, 2.9)
	8	-3.2	38	-1.6	1.5	(-2.0, 5.1)
	10	-4.1	37	-2.8	1.3	(-3.5, 6.2)
	12	-6.2	39	-2.1	4.1	(-0.9, 9.1)
DAY 12 OF CYCLE 1	0.25	-1.2	38	-1.3	-0.2	(-5.1, 4.8)
	0.5	-3.5	38	-2.2	1.3	(-3.7, 6.3)
	1	-0.6	37	-4.2	-3.6	(-8.5, 1.2)
	2	-0.5	37	-2.2	-1.7	(-6.3, 2.9)
	4	-2.7	39	0.2	2.9	(-3.1, 8.9)
	6	-2.7	38	-3.2	-0.6	(-5.2, 4.1)
	8	-3.3	35	-0.6	2.7	(-2.3, 7.7)
	10	-4.1	36	-5.2	-1.1	(-6.9, 4.7)
	12	-6.1	35	-1.0	5.1	(-1.6, 11.9)

4.2.1.1 Assay Sensitivity Analysis

There is no assay sensitivity established because no positive control arm included.

4.2.1.2 Graph of ΔΔQTcI Over Time

Figure 3 and Figure 4 display the time profile of ΔΔQTcI for TAS-102 35 mg/m^2 b.i.d..

Figure 3: Mean and 90% CI ΔΔQTcI Time Course for Day 1 Cycle 1

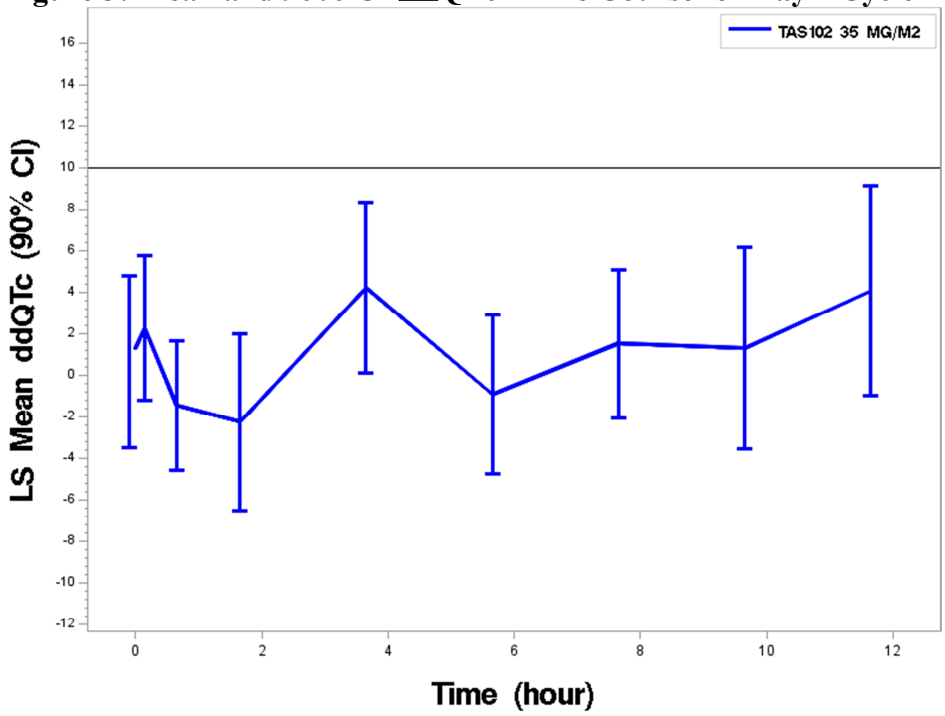
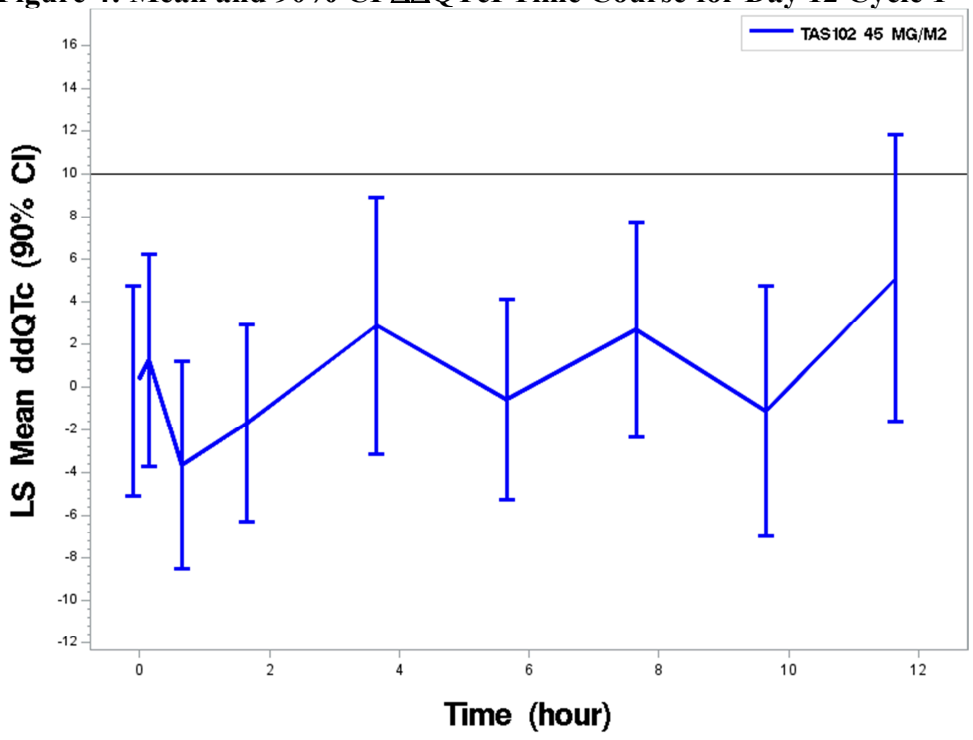


Figure 4: Mean and 90% CI ΔΔQTcI Time Course for Day 12 Cycle 1



4.2.1.3 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. Two subjects' QTcF are above 500 ms.

Table 9: Categorical Analysis for QTcI

	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
Treatment Group					
TAS102 35 MG/M^2	42	31 (73.8%)	8 (19.0%)	1 (2.4%)	2 (4.8%)

Table 10 lists the categorical analysis results for ΔQTcI. One subject's change from baseline is above 90 ms.

Table 10: Categorical Analysis for ΔQTcI

	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
Treatment Group					
TAS102 35 MG/M^2	42	41 (97.6%)	0 (0.0%)	1 (2.4%)	0 (0.0%)

4.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between TAS-102 35 mg/m^2 b.i.d. and placebo are 4.6 bpm and 6.8 bpm on Day 1 Cycle 1 and Day 12 Cycle 1, respectively. Table 12 presents the categorical analysis of HR. Twelve subjects who experienced HR interval greater than 100 bpm are in TAS-102 dosed-group.

Table 11: Analysis Results of ΔHR and ΔΔHR for TAS-102 35 mg/m^2 BID on Day 1 Cycle 1 and Day 12 Cycle 1

		Treatment Group				
		Placebo	TAS102 35 MG/M^2			
		ΔHR	ΔHR		ΔΔHR	
Day/Cycle	Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
DAY 1 OF CYCLE 1	0.25	0.5	39	2.7	2.2	(-0.3, 4.6)
	0.5	0.0	39	1.5	1.5	(-1.1, 4.1)
	1	-0.2	40	-0.3	-0.1	(-2.6, 2.4)
	2	0.3	37	0.1	-0.2	(-2.9, 2.5)
	4	0.8	39	0.1	-0.7	(-3.2, 1.8)
	6	2.2	36	3.3	1.0	(-2.1, 4.1)
	8	-0.4	38	0.6	1.1	(-1.5, 3.6)
	10	0.7	37	0.4	-0.3	(-3.5, 2.9)
	12	3.3	39	3.4	0.1	(-3.5, 3.6)
DAY 12 OF CYCLE 1	0.25	0.6	38	4.4	3.7	(0.7, 6.8)
	0.5	0.0	38	2.9	2.9	(-0.1, 5.8)
	1	-0.3	37	2.7	3.0	(0.0, 6.0)
	2	0.4	37	3.3	2.9	(-0.1, 5.9)
	4	0.8	39	2.4	1.6	(-1.9, 5.2)
	6	2.2	38	4.4	2.2	(-1.2, 5.7)
	8	-0.6	35	3.1	3.7	(0.6, 6.8)
	10	0.7	36	2.1	1.4	(-1.5, 4.3)
	12	3.5	35	4.2	0.7	(-2.9, 4.4)

Table 12: Categorical Analysis for HR

	Total N	HR <= 100 bmp	HR >100 bmp
Treatment Group			
TAS102 35 MG/M2	42	30 (71.4%)	12 (28.6%)

4.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between TAS-102 35 mg/m^2 b.i.d. and placebo are 6.5 ms and 4.0 ms on Day

1 Cycle 1 and Day 12 Cycle 1, respectively. Six subjects who experienced PR interval greater than 200 ms are in TAS-102 dosed-groups.

Table 13: Analysis Results of ΔPR and ΔΔPR for TAS-102 35 mg/m^2 BID on Day 1 Cycle 1 and Day 12 Cycle 1

		Treatment Group				
		Placebo	TAS102 35 MG/M^2			
		ΔPR	ΔPR		ΔΔPR	
Day/Cycle	Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
DAY 1 OF CYCLE 1	0.25	0.5	39	-0.7	-1.2	(-3.7, 1.2)
	0.5	1.7	39	0.7	-0.9	(-3.9, 2.1)
	1	0.5	40	1.0	0.5	(-1.9, 3.0)
	2	0.3	37	1.2	0.9	(-2.1, 3.9)
	4	0.0	39	0.7	0.7	(-2.8, 4.1)
	6	-0.2	36	-1.3	-1.1	(-4.6, 2.4)
	8	0.8	38	1.6	0.9	(-2.1, 3.8)
	10	0.3	37	-0.3	-0.6	(-3.5, 2.4)
	12	-4.3	39	-1.8	2.5	(-1.4, 6.5)
DAY 12 OF CYCLE 1	0.25	0.4	38	-3.6	-4.1	(-6.8, -1.3)
	0.5	1.7	38	-0.8	-2.5	(-5.4, 0.4)
	1	0.5	37	-1.0	-1.4	(-4.3, 1.4)
	2	0.2	37	-1.6	-1.8	(-5.4, 1.7)
	4	-0.0	39	-1.2	-1.2	(-4.8, 2.4)
	6	-0.3	38	-1.7	-1.4	(-5.1, 2.3)
	8	0.7	35	-1.0	-1.7	(-5.0, 1.6)
	10	0.2	36	-1.9	-2.1	(-5.2, 0.9)
	12	-4.6	35	-4.2	0.3	(-3.3, 4.0)

Table 14: Categorical Analysis for PR

	Total N	PR <= 200 ms	PR >200 ms
Treatment Group			
TAS102 35 MG/M2	42	36 (85.7%)	6 (14.3%)

4.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results

are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between TAS-102 35 mg/m^2 b.i.d. and placebo are 3.4 ms and 3.8 ms on Day 1 Cycle 1 and Day 12 Cycle 1, respectively. Table 16 presents the categorical analysis of QRS. One subject who experienced QRS interval greater than 110 ms is in TAS-102 dosed-group.

Table 15: Analysis Results of ΔQRS and ΔΔQRS QTcI for TAS-102 35 mg/m^2 BID on Day 1 Cycle 1 and Day 12 Cycle 1

		Treatment Group				
		Placebo	TAS102 35 MG/M^2			
		ΔQRS	ΔQRS		ΔΔQRS	
Day/Cycle	Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI
DAY 1 OF CYCLE 1	0.25	-0.0	39	0.3	0.4	(-2.3, 3.0)
	0.5	0.4	39	1.2	0.8	(-1.7, 3.4)
	1	0.2	40	-0.0	-0.2	(-2.7, 2.3)
	2	1.2	37	0.3	-0.9	(-3.5, 1.7)
	4	1.3	39	2.2	0.9	(-1.4, 3.1)
	6	-0.5	36	0.4	0.9	(-1.2, 2.9)
	8	-0.4	38	0.7	1.1	(-1.3, 3.5)
	10	0.1	37	0.1	0.0	(-2.4, 2.5)
	12	1.5	39	-0.3	-1.8	(-4.8, 1.1)
DAY 12 OF CYCLE 1	0.25	-0.0	38	1.0	1.0	(-1.8, 3.8)
	0.5	0.4	38	-0.1	-0.6	(-3.1, 2.0)
	1	0.2	37	-0.7	-0.9	(-3.6, 1.8)
	2	1.3	37	0.3	-1.0	(-3.6, 1.5)
	4	1.3	39	1.2	-0.2	(-2.4, 2.0)
	6	-0.4	38	-0.7	-0.3	(-2.6, 2.1)
	8	-0.4	35	-0.6	-0.3	(-2.6, 2.1)
	10	0.1	36	-1.5	-1.7	(-4.2, 0.9)
	12	1.5	35	-0.2	-1.7	(-4.7, 1.4)

Table 16: Categorical Analysis for QRS

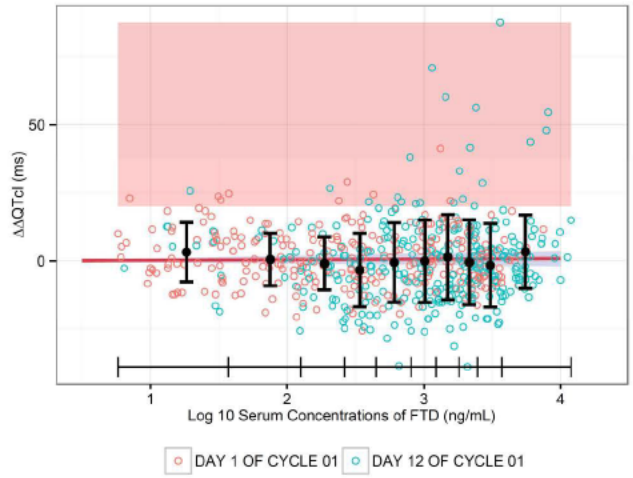
	Total N	QRS <= 110 ms	QRS > 110 ms
Treatment Group			
TAS102 35 MG/M2	42	41 (97.6%)	1 (2.4%)

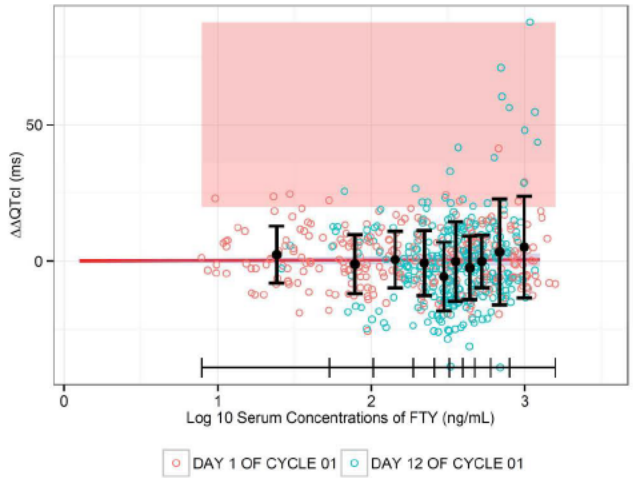
4.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Error! Reference source not found. The relationship between ΔΔQTcI and FTD, FTY, and TPI (free) log10 concentrations is visualized in Figure 5 with no evident exposure-response relationship. Exposure response analysis was conducted using linear mixed effect model with subject as random effect. Intercept was fixed to 0. Confidence intervals around estimates of slope were calculated with a nonparametric bootstrap, (n=500). None of the three estimated slopes was significantly positive (P>0.05).

The relationships between ΔQTcI and FTD, FTY, and TPI (free) log10 concentrations are also explored because we previously considered that the study design was not ideal to minimize any period effect between days on placebo and days on drug treatment. As shown in Figure 6, there are no apparent exposure-response relationships for ΔQTcI.

Figure 5: ΔΔQTcI vs. FTD, FTY, and TPI (free) log10 concentrations





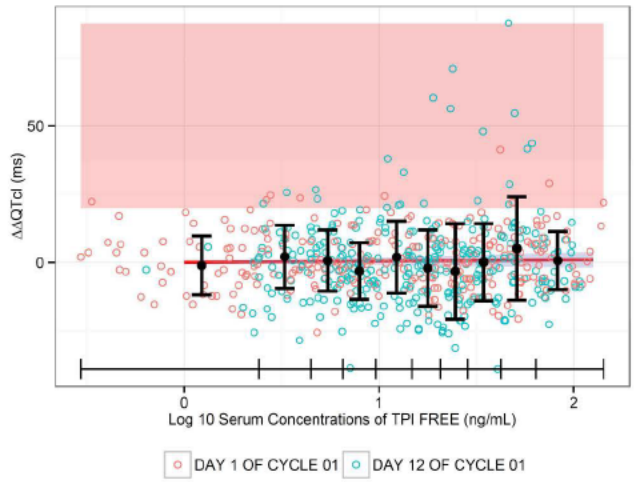
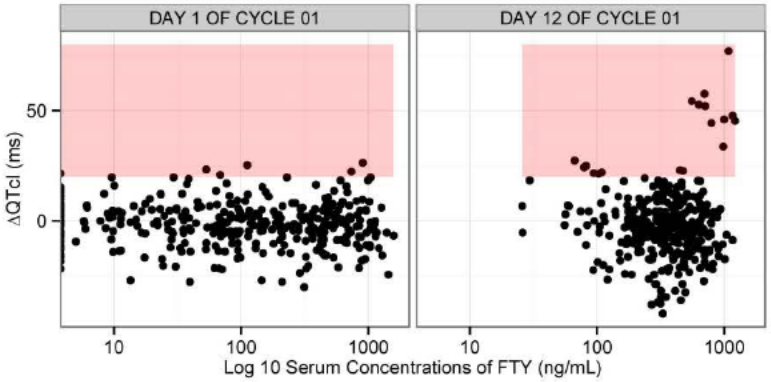
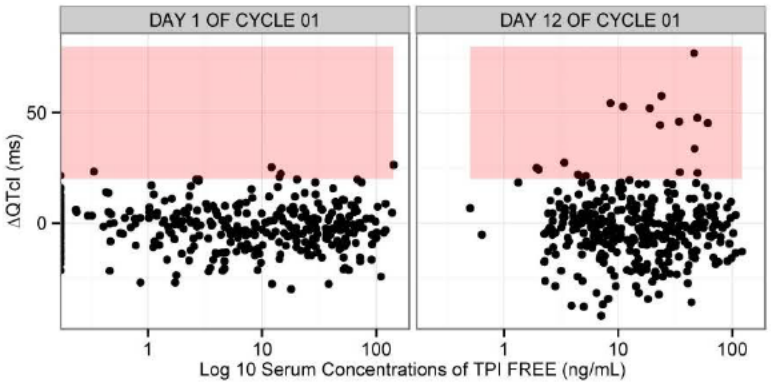
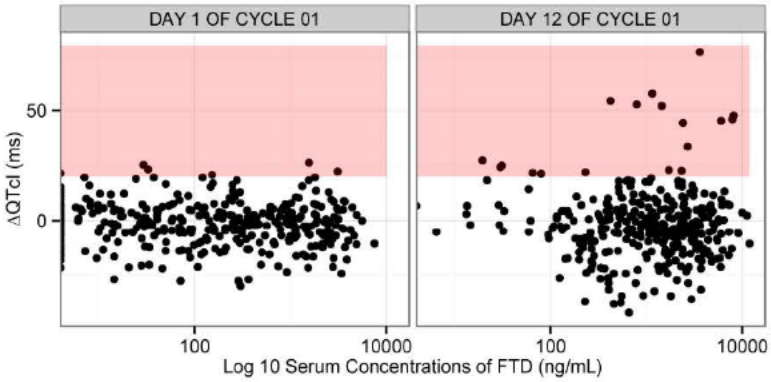


Figure 6. ΔQTcI vs. FTD, FTY, and TPI (free) log10 concentrations







4.4 CLINICAL ASSESSMENTS

4.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines, i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

4.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

4.4.3 PR and QRS Interval

There were no clinically relevant effects on PR or QRS.

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The recommended starting dose of TAS-102 for adults is 35 mg/m^2/dose administered twice daily, after the morning and the evening meal, 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.	
Maximum tolerated dose	In a Japanese Phase 1 study of primarily colorectal cancer patients (85.7%), the MTD was not reached at the 35 mg/m^2/dose BID level, but a greater than 35 mg/m^2/dose BID was not tested due to hematologic toxicities observed at this dose. In a Phase I study subsequently conducted in the US on CRC patients (100%), the tolerability of the 35 mg/m^2/dose BID of TAS-102 was similar to that observed in Japanese patients; and likewise, a dose greater than	
Principal adverse events	The most frequent adverse events reported with TAS-102 are those of myelosuppression (anemia, neutropenia/ neutrophil count decreased, thrombocytopenia, and leucopenia/WBC decreased) and gastrointestinal symptoms (nausea, vomiting and diarrhea). Other frequently reported events include fatigue and decreased appetite.	
Maximum dose tested	Single Dose	35 mg/m^2
	Multiple Dose	35 mg/m^2 BID for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle) repeated every 4 weeks
Exposures achieved at maximum tested dose	Single Dose (Cycle 1 Day 1)	Analyte C_{max} Mean (%CV) FTD 2381.21 ng/mL (43.99%) FTY 764.89 ng/mL (26.34%) TPI 68.68 ng/mL (43.25%) Analyte AUC_{inf} Mean (%CV) FTD 7119.92 ng*hr/mL (33.88%) FTY 3435.59 ng*hr/mL
	Multiple Dose (Cycle 1 Day 12)	Analyte C_{max} Mean (%CV) FTD 4857.06 ng/mL (39.74%) FTY 678.76 ng/mL (29.43%) TPI 69.35 ng/mL (39.58%) Analyte $AUC_{0\text{-last}}$ Mean (%CV) FTD 23696.93 ng*hr/mL (31.31%) FTY 5206.27 ng*hr/mL

Range of linear PK	Single dose PK parameters: FTD: C_{max} was linear but AUC was not linear in the dose range of 15~35 mg/m^2. Dose-normalized AUC was comparable in the dose range of 20~35 mg/m^2. TPI: C_{max} and AUC were linear in the dose range of 15~35 mg/m^2	
Accumulation at steady state	Dosing regimen: 35 mg/m^2 BID for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle) repeated every 4 weeks. Accumulation (Cycle 1 Day 12 vs Cycle 1 Day 1): • FTD $AUC_{0\text{-last}}$: approximately 3-fold • FTD C_{max}: approximately 2-fold No further accumulation for FTD with successive cycles • TPI $AUC_{0\text{-last}}$: no accumulation • TPI C_{max}: no accumulation	
Metabolites	TAS-102 component: Activity FTD; Inactive TPI Primary Metabolite: FTY; 6-hydroxymethyluracil	
Absorption	Absolute/Relative Bioavailability	The relative bioavailability of the TAS-102 tablet compared to an oral solution: Analyte $AUC_{0\text{-last}}$: FTD 1.004 (0.926 - 1.089); TPI 0.960 (0.859
	T_{max} (Cycle 1 Day 1)	Analyte: Median (range) FTD 1.50 hr (0.53, 4.00); FTY 3.00 hr (1.00, 6.08); TPI 3.00
Distribution	Vd/F (Cycle 1 Day 1)	Analyte: Mean (%CV) FTD 20.92 L (46.26%); TPI 332.95
	Plasma protein binding (% bound)	Analyte: Range(%) FTD 0.5~50 µg/mL 96.7~97.3%; TPI 0.05~5 µg/mL

Elimination	Route	Primary route; percent dose eliminated FTD: Urinary excretion of unchanged FTD was limited; absorbed FTD was mainly metabolized to FTY and excreted into urine. TPI: Absorbed TPI was mainly excreted as unchanged form in urine. Analyte Ae% Mean FTD 1.5% FTY 19.2% TPI
	Terminal t½ (Cycle 1 Day 1)	Analyte Mean (%CV) FTD 1.42 hr (29.52%) FTY 1.76 hr (21.49%) TPI
	CL/F (Cycle 1 Day 1)	Analyte Mean (%CV) FTD 10.53 L/hr (42.34%) TPI 109.33
Intrinsic factors	Age	Based on a population pharmacokinetic analysis, the pharmacokinetics of FTD and TPI are not expected to be affected by age.
	Sex	Based on a population pharmacokinetic analysis, the pharmacokinetics of FTD and TPI are not expected to be affected by sex. The apparent difference in Vd/F seen for gender is attributable to the difference in body size, which is adjusted for by BSA dosing of
	Race	Based on a population pharmacokinetic analysis, the pharmacokinetics of FTD and TPI are not expected to be affected by race. The potential ethnic difference in body size is adjusted for by
	Hepatic and Renal Impairment	Hepatic impairment Based on a population pharmacokinetic analysis, liver function parameters including SGOT, SGPT, ALP, and T-Bil were not significant covariates for PK parameters of either FTD or TPI. Therefore, the pharmacokinetics of FTD and TPI are not expected to be affected by hepatic impairment.

Intrinsic factors (continued)	Hepatic and Renal Impairment	Renal impairment Based on a population pharmacokinetic analysis, the mean relative ratio of FTD AUC in patients with mild (CLcr = 60-89 mL/min) and moderate (CLcr = 30-59 mL/min) renal impairment compared to patients with normal renal function (median CLcr = 103 mL/min) in this population, were estimated to be 1.07~1.32 and 1.32~1.87, respectively, using the final model developed for CL/F of FTD. $CL/F = 2.93 \times (CLcr/103)^{0.507} \times (ALB/3.90)^{-0.633} \times \exp(\eta_{i, CL/F})$ Based on the same exercise as above, the mean relative ratio of TPI AUC in patients with mild (CLcr = 60-89 mL/min) and moderate (CLcr = 30-59 mL/min) renal impairment compared to patients with normal renal function (median CLcr = 103 mL/min) in this population, were estimated to be 1.09~1.38 and
Extrinsic factors	Drug Interactions	No clinical drug interaction studies have been conducted. Based on a population pharmacokinetic analysis, OCT2 inhibitors did not have any significant effects on the
	Food Effects	AUC of FTD was not affected by food intake (high fat meal), while C_{max} of FTD, C_{max} and AUC of TPI were decreased by approximately 40%. In the majority of patients in clinical studies, TAS-102 was administered within 1 hour after completion of morning and evening meals. Therefore, it is recommended that TAS-102 should be administered within 1 hour after completion of morning and evening meals. FTD Ratio geometric mean (Fed/Fasted, 90% CI) C_{max} 0.6074 (0.5037 ～ 0.7323) AUC_{0-12} 0.9560 (0.8566 ～ 1.0670) AUC_{inf} 0.9559 (0.8556 ～ 1.0680) TPI Ratio geometric mean (Fed/Fasted, 90% CI) C_{max} 0.5578 (0.4732 ～ 0.6576) AUC_{0-12} 0.5526 (0.4802 ～ 0.6358) AUC_{inf} 0.5581 (0.4872

Expected high clinical exposure scenario	Severe renal impairment: If a patient with severe renal impairment (CLcr = 15~29 mL/min) received TAS-102 35 mg/m^2, the mean relative ratio of daily AUC compared to patients with normal renal function (median CLcr = 103 mL/min) in the patient population analyzed, is estimated to be 1.90~2.66, using the final model developed for CL/F of FTD. FTD CL/F = $2.93 \times (\text{CLcr}/103)^{0.507} \times (\text{ALB}/3.90)^{-0.633} \times \exp(\eta_{i,\,CL/F})$
Preclinical Cardiac Safety	• FTD had no effect on hERG current at concentrations up to 300 µmol/L. • Oral administration of FTD at dose levels of up to 108.8 mg/kg produced no effects on assessed cardiovascular parameters in the conscious monkey. • TPI had no effect on hERG current at concentrations up to 100 µmol/L. • Oral administration of TPI at dose levels of up to 1000 mg/kg produced no effects on assessed cardiovascular parameters in the conscious monkey.
Clinical Cardiac Safety	The cardiac safety study investigated the effect of TAS-102 on cardiac repolarization, evaluated the cardiac safety profile of TAS-102. Forty-four (44) patients were enrolled in the study. In the cardiac safety portion of the study, patients were given a single blind oral placebo dose on Day -1; TAS-102 35 mg/m^2 oral BID was given on Days 1-5 and 8-12, rest Days 13-28 (end of cycle). There were no treatment emergent adverse events of QT prolongation, syncope, seizure, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, flutter, torsades de pointes or sudden

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/s/

DINKO REKIC
12/03/2014

JIANG LIU
12/03/2014

MOH JEE NG
12/03/2014

QIANYU DANG
12/03/2014

MICHAEL Y LI
12/03/2014

NORMAN L STOCKBRIDGE
12/03/2014

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/s/

GINA M DAVIS
09/09/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 3, 2015
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carole Broadnax, RPh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LONSURF (trifluridine and tipiracil)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	207981
Applicant:	Taiho Oncology, Inc.

1 INTRODUCTION

On December 19, 2014, Taiho Oncology, Inc. submitted for the Agency's review a New Drug Application (NDA) 207981 for LONSURF (trifluridine and tipiracil) tablets. The proposed indication for LONSURF (trifluridine and tipiracil) is for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on December 24, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), for LONSURF (trifluridine and tipiracil) tablets.

2 MATERIAL REVIEWED

- Draft LONSURF (trifluridine and tipiracil) PPI received on December 19, 2014, and received by DMPP on August 24, 2015.
- Draft LONSURF (trifluridine and tipiracil) PPI received on December 19, 2014, and received by OPDP on August 19, 2015.
- Draft LONSURF (trifluridine and tipiracil) Prescribing Information (PI) received on December 19, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 24, 2015.
- Draft LONSURF (trifluridine and tipiracil) Prescribing Information (PI) received on December 19, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 19, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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/s/

MORGAN A WALKER
09/03/2015

CAROLE C BROADNAX
09/03/2015

LASHAWN M GRIFFITHS
09/03/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

To: Gina Davis, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Date: September 2, 2015

Re: **LONSURF (trifluridine and tipiracil) tablets, for oral use**
NDA 207981
Comments on proposed product labeling (Package Insert, Patient Package Insert and carton/container)

In response to the Division of Oncology Products 2 (DOP 2)'s December 24, 2014, consult request, OPDP has reviewed proposed product labeling (Package Insert (PI) and carton/container) for LONSURF (trifluridine and tipiracil) tablets, for oral use. The version of the substantially complete PI used in this review was obtained from a link to SharePoint that was sent via electronic mail from DOP-2 on August 19, 2015, and is titled, "081915 Lonsurf SCPI – NDA 207981 – Taiho – post internal labeling meeting 7.23.15 doc.docx." The version of the carton and container labeling used in this review was obtained from a link to the EDR (submission 0023) that was sent via electronic mail from DOP 2 on August 24, 2015.

OPDP's comments for the PI are provided directly in the attached PDF document. OPDP does not have any comments on the carton and container labeling at this time.

OPDP's comments on the proposed Patient Package Insert will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
09/02/2015

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2014

BACKGROUND: This New Drug Application (NDA) is for full approval of Lonsurf [Proposed] (trifluridine/tipiracil) for the "treatment of patients with metastatic colorectal cancer 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 NDA will be supported by efficacy and safety data from the following pivotal study based on overall survival (OS) results:

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

The NDA will also include the efficacy and safety data from the following supportive studies:

- Study J003-10040030: entitled "Placebo-Controlled, Multicenter, Double-Blind, Randomized, Phase II Study of TAS-102 in Patients with Unresectable Advanced or Recurrent Colorectal Cancer Who Have Had 2 or More Chemotherapy Regimens and Who Are Refractory or Intolerant to Fluoropyrimidine, Irinotecan, and Oxaliplatin."

- Study J001-10040010 entitled, "TAS-102 Phase I Clinical Study in Patients with Solid Tumors."

- Study J004-10040040 entitled, "Clinical Pharmacology Study of Food Effect on TAS-102."

- Study TPU-TAS-102-101 entitled, "A Phase 1, Open-label, Non-randomised, Dose finding, Safety and Tolerability Study of Orally Administered TAS-102 in Patients with Refractory Metastatic Colorectal Cancer."

- Study TPU-TAS-102-102 entitled, "A Phase 1, open-label, randomised, parallel group study evaluating the pharmacokinetics of trifluridine (FTD) as a component of TAS-102 compared with FTD alone."

- Study TPU-TAS-102-103 entitled, "A Phase 1 study to evaluate the cardiac safety of orally administered TAS-102 in patients with advanced solid tumours."

- Study TPU-TAS-102-104 entitled, "A Phase 1, open-label, randomised, crossover study evaluating the bioavailability of TAS-102 tablets relative to an oral solution containing equivalent amounts of trifluridine (FTD) and tipiracil hydrochloride (TPI)."

Regulatory History:

On March 24, 2014, Oncology, Inc. (Taiho) received approval in Japan for Lonsurf [Proposed] (trifluridine/tipiracil) for the treatment of patients with unresectable advanced or recurrent colorectal cancer (mCRC). This approval was based on the results of the randomized (2:1), double-blind placebo controlled clinical trial conducted in Japan (J003-10040030). The primary endpoint of the trial was overall survival and the primary endpoint was tested with a one-sided alpha of 0.10. Data from this study is proposed for supportive data for the US NDA application.

The regulatory history in the US includes the following: initial development program for the trifluridine/tipiracil began in 1998 in solid tumors; development was suspended in 2009 and reinitiated in 2011; an EOP2 CMC only meeting was held on November 29, 2011; an EOP2 multidiscipline meeting was held December 12, 2011, regarding the data from studies conducted in Japan and seeking feedback on the proposed clinical development plan for treatment of colorectal cancer; new registrational Protocol TPU-TAS-102-301 (RECOURSE) submitted on May 24, 2012; a Pre-NDA CMC only meeting scheduled for December 5, 2013, but cancelled by the sponsor as the information in the preliminary document was sufficient, and a Pre-NDA multidiscipline meeting was held July 31, 2014, to discuss the content and format of the NDA and obtain agreement on any late components of an application.

Finally, Taiho was granted Fast Track Designation for patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy to demonstrate an improvement in overall survival on September 12, 2014.

Taiho submitted the first piece of the application (rolling review submission) on November 7, 2014, with the final component submitted December 19, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gina Davis	Y
	CPMS/TL:	Melanie Pierce	Y
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Leigh Marcus	Y
	TL:	Steven Lemery	Y

Social Scientist Review (*for OTC products*)	Reviewer:	N/A	____
	TL:	N/A	____
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	____
	TL:	N/A	____
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	____
	TL:	N/A	____
Clinical Pharmacology	Reviewer:	Xianhua Cao	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Weishi Yuan	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sachia Khasar	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	____
	TL:	N/A	____
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	N/A	____
	TL:	N/A	____
Product Quality (CMC)	Reviewer:	Erika Englund – DS Rajiv Agarwal - DP	Y Y
	TL:	Olen Stephens	Y
Biopharmaceutics	Reviewer	Salaheldin Hamed	Y
	TL:	Olen Stephens	Y
Quality Microbiology	Reviewer:	Quamrul Majumder	Y
	TL:	Olen Stephens	Y
CMC Labeling Review	Reviewer:		
	TL:		

Facility Review/Inspection	Reviewer:	To be determined	
	TL:	To be determined	
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	_____
	TL:	N/A	_____
Pharmacometrics	Reviewer:	Jingyu Yu	Y
	TL:	Liang Zhao	Y
Other attendees	Liang Zhou Meredith Libeg		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues:	☒ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain: N/A	
• Electronic Submission comments **List comments**: N/A	☒ Not Applicable ☐ No comments
CLINICAL Labeling comments were sent to the sponsor on February 5, 2015. **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☐ To be determined Reason: ○ **this drug is not the first in its class** ○ **the clinical study design was acceptable** ○ **the application did not raise significant safety or efficacy issues** ○ **the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease**
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) CMC comments/request to be communicated to the sponsor in the filing letter. **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO - see comment below ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES – see comment below ☐ NO ☐ YES ☒ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, M.D. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 13, 2015 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: Preliminary labeling comments sent to Taiho on February 5, 2015 and CMC comments/deficiencies included in the filing letter.	

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
N/A	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). – **N/A**
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. **N/A**
N/A	351(k) BLA/supplement: If filed, send filing notification letter on day 60 –**N/A**
N/A	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier) **This application will be reviewed under PDUFA V standard timelines.**
☒	Send review issues/no review issues by day 74 **CMC deficiencies will be included in the 60-day filing letter.**
☒	Conducted a PLR format labeling review and include labeling issues in the Filing Letter. **Labeling issues were conveyed in an email communication dated 2/5/15.**
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☒	Other - Taiho stated, in an email communication dated February 11, 2015, that the Drug Inspection Branch will not be able to schedule the inspection of the manufacturing site until May at the earliest and potentially as late as July.

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/s/

GINA M DAVIS
08/13/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 10, 2015

TO: Gina Davis, Regulatory Health Project Manager
Leigh Marcus, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH**:** Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207981

APPLICANT: Taiho Oncology, Inc.

DRUG: Lonsurf (TAS-102)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION(S): For the treatment of metastatic colorectal cancer.

CONSULTATION REQUEST DATE: December 4, 2014
INSPECTION SUMMARY GOAL DATE: October 24, 2015 (Revised: August 24, 2015)
DIVISION ACTION GOAL DATE: [on or before] December 19, 2015
PDUFA DATE: December 19, 2015

I. BACKGROUND:

Taiho Oncology, Inc. [Taiho] seeks approval to market Lonsurf (TAS-102) for the treatment of patients with unresectable advanced or recurrent (metastatic) colorectal cancer (mCRC). TAS-102 is an oral combination anticancer drug of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

The key study supporting this application is Study TPU-TAS-102-301 (RECOURSE). This study was a multinational, double-blind, two-arm, parallel, randomized Phase 3 comparison study evaluating the efficacy and safety of TAS-102 versus placebo in patients with refractory metastatic colorectal cancer. Patients were randomly assigned (2:1) to TAS-102 (experimental arm) or placebo (control arm). The trial enrolled 800 patients who received at least two prior regimens of standard chemotherapies for mCRC and were refractory to, or failed, those chemotherapies. The trial was conducted in North America, Europe, Japan, and Australia. Patients were randomly assigned to receive either TAS-102 or placebo in order to investigate the efficacy of TAS-102. The primary objective of the RECOURSE trial was improvement in overall survival (OS) versus placebo.

The study was conducted at 101 centers in the United States (21), Western Europe (54), Asia Pacific/Japan (20), Australia (5), and Czechoslovakia (1). The study was conducted under IND 57674.

Six clinical sites were chosen for inspection: Site 356 (Dr. Rocio Carbonero, Sevilla, Spain), Site 355 (Dr. Josep Tabernero, Barcelona, Spain), Site 604 (Dr. Alfredo Falcone, Pisa, Italy), Site 706 (Dr. Tadamichi Denda, Chiba, Japan), Site 704 (Dr. Kensei Yamaguchi, Saitama, Japan), and Site 705 (Dr. Takayuki Yoshino, Chiba, Japan) based on enrollment of large numbers of study subjects, and significant primary efficacy results pertinent to decision making. This would be the first approval of this new drug and a significant amount of the experience with this drug has been at foreign sites.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Rocio Carbonero Avenida Manuel Siurot s/n. Servicio Oncologia Sevilla, 41013 Spain	Protocol: TPU-TAS-102-301 Site Number: 356 Number of Subjects: Enrolled: 21	March 16-18, 2015	NAI
CI#2: Josep Tabernero, Passeig de la Vall d'Hebrón 1 19-129 Barcelona, 08035 Spain	Protocol: TPU-TAS-102-301 Site Number: 355 Number of Subjects: Enrolled: 20	March 9-11, 2015	NAI
CI#3: Alfredo Falcone, Ospedale Santa Chiara Via Roma 67 Polo Oncologico, Edificio 22 Pisa, Italy 67 56126	Protocol: TPU-TAS-102-301 Site Number: 604 Number of Subjects: Enrolled: 35	March 16-20, 2015	NAI
CI#4: Tadamichi Denda, 666-2 Nitona-cho Chuo-ku Chiba-city, Chiba 2608717 Japan	Protocol: TPU-TAS-102-301 Site Number: 706 Number of Subjects: Enrolled: 14	March 16-18, 2015	NAI
CI#5: Kensei Yamaguchi, 780 Komuro Inamachi Kita-adachi-gun, Saitama 3620806 Japan	Protocol: TPU-TAS-102-301 Site Number: 704 Number of Subjects: Enrolled: 15	March 23-25, 2015	NAI
CI#6: Takayuki Yoshino, 6-5-1 Kashiwanoha Kashiwa-city, Chiba 2778577 Japan	Protocol: TPU-TAS-102-301 Site Number: 705 Number of Subjects: Enrolled: 30	March 30-April 1, 2015	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: Dr. Rocio Carbonero (Site 356)**

a. **What was inspected:** The site screened twenty seven subjects, and twenty one were enrolled. At the time of this inspection all subjects had completed cycle 1; nineteen subjects eventually discontinued due to disease progression; one subject discontinued due to an adverse event, and one subject became ineligible to continue when they decided to initiate radiotherapy (voluntarily withdrew). Study records of all twenty seven screened subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207981, focusing on protocol compliance, adverse events, efficacy evaluations, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring records.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary and secondary efficacy endpoints were verified. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. There was no evidence of underreporting of adverse events. Several minor deficiencies were noted and discussed with the site staff. Briefly, the consent process (for the consent addendum) was conducted for one subject by a fellow, who was not listed on the delegation of responsibility log. The CI had initialed the progress notes for this visit indicating that they were present overseeing the fellow. The date of consent was entered into the eCRF incorrectly for one subject. The correct date was May 8, 2013, and it was entered into the eCRF as May 10, 2013. One subject's source folder was missing the source document for disease progression but this was readily obtained from the hospital's electronic medical records. A Form FDA 483 was not issued.

c. **Assessment of data integrity:** The data for Dr. Carbonero's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

2. CI#2: Dr. Josep Tabernero (Site 355)

a. What was inspected: The site screened twenty seven subjects, and twenty were enrolled. At the time of this inspection all subjects had completed cycle 1; 4 subjects discontinued prior to starting cycle 2 due to disease progression. The remaining 16 subjects participated in additional cycles. Study records of all twenty seven screened subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 207981, focusing on protocol compliance, adverse events, efficacy evaluations, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring records.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary and secondary efficacy endpoints were verified. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. There was no evidence of underreporting of adverse events. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Tabernero's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

3. CI#3: Dr. Alfredo Falcone (Site 604)

a. What was inspected: The site screened thirty eight subjects. Three were screen failures and the remaining thirty five were enrolled. Study records of all screened subjects were audited. The record audit included informed consent documents, comparison of source documentation to CRFs and data listings submitted to NDA 207981, focusing on protocol compliance, baseline data, entry criteria assessments, protocol-specified periodic laboratory test results, all study treatments and follow up visit data. The record audit also assessed adverse events, efficacy evaluations, reporting of AEs in accordance with the protocol, protocol deviations, test article accountability, and monitoring records. Training records, delegations of authority logs, sponsor correspondence and IRB correspondence, and test article storage temperature and calibration logs for the IP storage unit were also assessed.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be good. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The inspection showed that subjects were appropriately consented and met enrollment criteria. The site conducted the study according to the protocol. The primary and secondary efficacy endpoints, overall survival and progression free

survival, respectively, were verified for all study subjects. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, drug accountability and protocol compliance found no major discrepancies. There was no evidence of underreporting of adverse events. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Falcone's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

4. CI#4: Dr. Tadamichi Denda (Site 706)

a. What was inspected: The site screened sixteen subjects, two were screen failures, and the remaining fourteen subjects were enrolled. All fourteen subjects had completed at least one cycle of study treatment. Study records of all subjects were audited. The record audit included the study site staff roles and responsibilities, credentials, investigator's agreement, financial disclosure statements, training records, protocol and consent document approvals by the local Ethics Committee/IRB, signed informed consent forms for all screened subjects, subject enrollment log, entry criteria for all screened subjects, screen failures, subject randomization for all enrolled subjects, AEs and SAEs, test article accountability, and monitoring records.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be very good. Records and procedures were clear, and extremely well organized. The primary and secondary efficacy endpoints, overall survival and progression free survival, respectively, were verified for all study subjects. No major deficiencies were noted. Adverse event (AE) records were reviewed for all subjects. Of the fourteen study subjects enrolled, three had experienced at least one SAE during the course of the study. The adverse events were captured in the patient charts and in the SAE CRFs. There was no evidence of underreporting of AEs or SAEs. Review of source documentation for consent, eligibility, randomization, treatment regimens, periodic protocol-specified assessments and study drug administration cycles found no major discrepancies compared to the datalistings submitted to NDA 207981. On-site monitoring was conducted by the Contract Research Organization, (b) (4) contracted by the sponsor, Taiho Oncology, Inc., Japan. The monitoring visit sign-in log was reviewed. Regular periodic monitoring visits were conducted at intervals of approximately once per week. No major deficiencies were identified. Assessment of drug storage and accountability found no deficiencies. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Denda's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

5. CI#5: Kensei Yamaguchi (Site 704)

a. What was inspected: The site screened fifteen subjects, and all fifteen subjects were enrolled. All subjects had completed at least one cycle of study treatment. Study records of all fifteen subjects were audited. The record audit included the study site staff roles and responsibilities, credentials, investigator's agreement, financial disclosure statements, training records, protocol and consent document approvals by the local Ethics Committee/IRB, signed informed consent forms for all screened subjects, subject enrollment log, entry criteria for all screened subjects, screen failures, subject randomization for all enrolled subjects, AEs and SAEs, test article accountability and monitoring records.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be very good. Records and procedures were clear, and extremely well organized. The primary and secondary efficacy endpoints, overall survival and progression free survival, respectively, were verified for all study subjects. No deficiencies were noted. Adverse event (AE) records were reviewed for all subjects. Of the fifteen study subjects enrolled, three had experienced at least one SAE during the course of the study. The adverse events were captured in the patient charts and in the SAE CRFs. There was no evidence of underreporting of AEs or SAEs. Review of source documentation for consent, eligibility, randomization, treatment regimens, periodic protocol-specified assessments, and study drug administration cycles found no major discrepancies compared to the data listings submitted to NDA 207981. On-site monitoring was conducted by the Contract Research Organization, (b) (4) contracted by the sponsor, Taiho Oncology, Inc., Japan. The monitoring visit sign-in log was reviewed. Regular periodic monitoring visits were conducted at intervals of approximately once per week. No major deficiencies were identified. Assessment of drug storage and accountability found no deficiencies. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Yamaguchi's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

6. CI#6: Takayuki Yoshino (Site 705)

a. What was inspected: The site screened thirty three subjects, three were screen failures, and the remaining thirty subjects were enrolled and completed at least one cycle of study drug therapy. Study records of all subjects were audited.

The record audit included the study site staff roles and responsibilities, credentials, investigator's agreement/Form FDA 1572's, financial disclosure statements, training records, protocol and consent document approvals by the local Ethics Committee/IRB, signed informed consent forms for all screened subjects, subject enrollment log, entry criteria for all screened subjects, screen failures, subject randomization for all enrolled subjects, AEs and SAEs, test article accountability, and monitoring records.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be very good. Records and procedures were clear, and extremely well organized. The primary and secondary efficacy endpoints, overall survival and progression free survival, respectively, were verified for all study subjects. No deficiencies were noted. Adverse event (AE) records were reviewed for all subjects. Of the thirty study subjects enrolled, eleven had experienced at least one SAE during the course of the study. The adverse events were captured in the patient charts and in the SAE CRFs. There was no evidence of underreporting of AEs or SAEs. Review of source documentation for consent, eligibility, randomization, treatment regimens, periodic protocol-specified assessments, and study drug administration cycles found no major discrepancies compared to the datalistings submitted to NDA 207981. On-site monitoring was conducted by the Contract Research Organization, (b) (4) contracted by the sponsor, Taiho Oncology, Inc., Japan. The monitoring visit sign-in log was reviewed. Regular periodic monitoring visits were conducted at intervals of approximately once per week beginning shortly after the first subject began treatment. No major deficiencies were identified. Assessment of drug storage and accountability found no deficiencies. A Form FDA 483 was not issued.

c. Assessment of data integrity: The data for Dr. Yoshino's site, associated with Study TPU-TAS-102-301 submitted to the agency in support of NDA 207981, appear reliable based on available information.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There were no trends in underreporting adverse events.

Based on the review of preliminary inspectional findings for Site 356 (Dr. Rocio Carbonero, Sevilla, Spain), Site 355 (Dr. Josep Tabernero, Barcelona, Spain), Site 604 (Dr. Alfredo Falcone, Pisa, Italy), Site 706 (Dr. Tadamichi Denda, Chiba, Japan), Site 704 (Dr. Kensei Yamaguchi, Saitama, Japan), and Site 705 (Dr. Takayuki Yoshino, Chiba, Japan), the Study TPU-TAS-102-301 data submitted to the Agency in support of NDA 207981, appear reliable and can be used in support of application.

{See appended electronic signature page}

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 17, 2015
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 207981
Product Name and Strength:	Lonsurf (trifluridine and tipiracil) Tablets, 15 mg/6.14 mg and 20 mg/8.19 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Taiho Oncology, Inc.
Submission Date:	February 19, 2015 and May 20, 2015
OSE RCM #:	2014-2488
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of the NDA review process for Lonsurf, DOP2 requested that we review the proposed container labels, carton labeling, and Prescribing Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This review identified that the proposed dosing regimen for Lonsurf is complex and could lead to dosing and administration errors. The recommended dose of Lonsurf would be administered orally as a 28-day cycle repeated every 4 weeks, as follows:

35 mg/m^2/dose orally twice daily X 5 days (Days 1 through 5), then
No doses X 2 days (Days 6 and 7), then
35 mg/m^2/dose orally twice daily X 5 days (Days 8 through 12), then
No doses X 2 days (Days 13 and 14), then
A 14-day rest period (Days 15 through 28).

Lonsurf is a dual-ingredient product, but dosing is based on the trifluridine component. This dosing regimen of Lonsurf is further complicated by a requirement that the dose be rounded to the nearest 5 mg and in some patients taking one or more tablets of differing strengths to obtain the prescribed dose. For example, a dose of 65 mg would require the patient to take two 20 mg/8.19 mg tablets plus one 15 mg/6.14 mg tablet. Since most state boards of pharmacy prohibit the co-mingling of tablets of different strengths in the same prescription vial,

pharmacists will be required to dispense the different strength tablets in its own prescription vial and label appropriately for patients who require dosing with both tablet strengths.

The proposed Lonsurf Prescribing Information does not adequately address the risk that this complicated regimen could confuse some patients and they could erroneously take more or less than prescribed. By taking an overdose, the patient could experience hematologic toxicities. By taking an underdose, the patient could not receive the full clinical benefits of the therapy.

Other drugs whose dosing regimens are also complex and may require patients to take capsule of differing strengths and amount that have resulted in fatal overdoses include lomustine and temozolomide. Both of these products are available in more than one strength capsule and may require the patient to take capsules of varying strengths to obtain the prescribed dose. As recent as the summer of 2014, the Institute on Safe Medication Practices reported on a patient who had taken a 3-month supply of Lomustine as a single dose. This overdose resulted in hematologic toxicities and ultimately the patient's death.[1]

In an effort to address the risk of patients taking the wrong number of capsules, both products have incorporated risk mitigation strategies. The labeling for both products contains warnings for both pharmacists and physicians.

For example, lomustine labeling includes instructions and warning in the following sections of the Prescribing Information: Dosage and Administration, Precautions, How Supplied, and Patient Information sections. In addition, Lomustine contains warnings on the carton labeling and container labels.

Temozolomide labeling includes the following labeling elements to address the risk of overdose of temozolomide: a table of suggested capsule combinations based on dose in the Dosing and Administration Section of the PI, a Patient Package Insert, and a Pharmacist Information Sheet.

Not each of these labeling elements is applicable for Lonsurf, but inclusion of some of these risk mitigation strategies or similar strategies could improve the proposed Lonsurf PI.

In addition to the issues listed above, the proposed dosing language in Section 2.1 (Recommended Dose) is confusing. The proposed language does not clearly state that the patient is to repeat twice daily doses for five days out of seven for two consecutive weeks. It also does not include information that the recommended dose is based on the trifluridine component of this dual-ingredient product.

[1] Institute for Safe Medication Practices. With oral chemotherapy, we simply must do better! ISMP Med Saf Alert Acute Care 2014 Jul 17;19(14):1.

We also noted that the Applicant has chosen to use National Drug Codes (NDCs) that have sequential product codes (middle digits). The NDCs are 64842-10 (b) (4)-X and 64842-10 (b) (4)-X for the 15 mg/6.14 mg tablet and the 20 mg/8.19 mg tablet, respectively. In addition, the net quantity statement is too close in proximity to the strength statement on container labels.

4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

1. Based on Applicant's May 20, 2015 response to DOP2's memorandum regarding changes to the container labels and carton labeling, we recommend all references to the product's dosage strength also include the tipiracil (b) (4). For example: Section 3 (Dosage Forms and Strengths) and Section 16 (How Supplied) tablet strengths are listed as (b) (4). Strength should be listed as 15 mg/6.14 mg and 20 mg/8.19 mg.

2. Add a reminder in Section 2.1 (Dosing and Administration) and Section 2.2 (Recommended Dose Modifications) for prescribers that dosing of this dual-ingredient product is based on the trifluridine component only and more clearly list the dosage regimen.

   For example, change the following statements:

   - (b) (4)
   - (b) (4) Round dose to the nearest 5 mg increment. (b) (4)
   - (b) (4)

   To read:

   - The recommended starting dose of Lonsurf in adults is 35 mg/m^2/dose (based on the trifluridine component) administered orally twice daily for 5 days of week one (Days 1 through 5) with 2 days rest (Days 6 and 7). Repeat twice daily dosing the first 5 days of week two (Days 8 through 12) with 2 days rest (Days 13 and

14). Followed by a 14-day rest period (Days 15 through 28). This 28-day treatment cycle is repeated every 4 weeks.

Treatment cycle					
Week 1		Week 2		Week 3	Week 4
Days 1 through 5 35 mg/m^2/dose orally twice daily	Days 6 and 7 No doses	Days 8 through 12 35 mg/m^2/dose orally twice daily	Days 13 and 14 No doses	Rest period No doses	

- Round the calculated dose to the nearest 5 mg increment. Do not exceed 80 mg/dose.

- If doses are missed, take the next scheduled dose as prescribed. Do not make up missed doses.

3. In section 2.2 (Recommended Dose Modifications), spell out "less than" rather than its corresponding symbol, <. The symbol, <, has been reported to be misinterpreted as greater than instead of the intended meaning less than. Certain abbreviations, acronyms, and symbols are dangerous and should not be used to avoid patient harm.[2] In addition, the abbreviation (b) (4) is used in this section for the first time in the PI. We defer to the review team on whether the abbreviation should be defined the first time it is used in the PI.

4. To address the potential for medication error in patients who are required to take both tablet strengths to obtain a prescribed dose, we recommend the following:
   a. Addition of a "Pharmacist Information" section to the PI to follow section 2.2 (Recommended Dose Modification).

   b. Addition of a statement in Section 17 (Patient Counseling Information) of the PI.

[2] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. (lines 521-544) Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

c. Addition of statements in the "How should I take LONSURF?" section of the Patient Information sheet (Patient Package Insert, PPI).

Pharmacist Information

Consider including the following information in this new section (used temozolomide Sandoz – authorized generic labeling as a reference):

2.3 Pharmacist Information

If a patient requires both LONSURF tablet strengths to obtain the prescribed dose:

- Dispense each strength of LONSURF in a separate bottle (one strength per one container).
- Make sure each bottle lists the strength per tablet.
- Counsel patient on the importance of taking the appropriate number of tablets of LONSURF from each bottle to provide the prescribed dose.

Patient Counseling

Add a statement to remind health care providers to convey this important safety information during patient counseling (used Temodar labeling as reference). For example,

Inform the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Inform the patient of the importance of reading prescription labels carefully and taking the appropriate number of capsules.

Patient Information

Consider adding statements that warn patients that Lonsurf is available in two strengths and they may need to take both strengths to obtain their prescribed dose. These statements should be added to the "How should I take LONSURF?" section of the PPI. We provide the following as an example; however, we defer to the Division of Medical Policy Programs – Patient Labeling Team for appropriate reading comprehension level and appropriate placement in the PPI.

<u>Example statements (used Temodar labeling as reference):</u>

Take LONSURF tablets exactly as prescribed.

LONSURF tablets come in two different strengths. Your doctor may prescribe both strengths of LONSURF tablets for you, so it is important that you understand how to take your medicine the right way. Be sure that you

understand exactly how many tablets you need to take on each day of your treatment, and what strengths to take. This may be different whenever you start a new cycle.

Talk to your doctor before you take your dose if you are not sure how much to take. This will help to prevent taking too much LONSURF and decrease your chances of getting serious side effects.

4.2 RECOMMENDATIONS FOR TAIHO ONCOLOGY, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. Health care professional sometimes refer to the product code (middle digits) of the National Drug Code (NDC) to identify the product. As currently presented, the product codes for Lonsurf 15 mg/6.14 mg bottles (64842-10 (b) (4) -X) and Lonsurf 20 mg/8.19 bottles (64842-10 (b) (4) -X) are sequential. The assignment of sequential numbers for the middle digits is not an effective differentiating feature. This can lead to wrong product or wrong strength errors. Therefore, revise the product code in the NDC numbers for each product to ensure the middle four digits are non-sequential[3].

2. Revise the statement on the side panels of container labels, "(b) (4) " to read, "Usual Dose: See prescribing information".

3. Relocate the net quantity statement such that it does not compete in prominence with the strength statement on the principal display panel (PDP). For example, switch the location of the net quantity and "Rx Only" statements (i.e., relocate the Rx Only statement to lower right hand corner of the PDP).

B. Carton Labeling

1. See comment A1 and A2.

[3] Guidance for industry, Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April, 2013

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lonsurf that Taiho submitted on February 19, 2015.

Table 2. Relevant Product Information for Lonsurf	
Initial Approval Date	N/A
Active Ingredient	trifluridine and tipiracil
Indication	Treatment of metastatic colorectal cancer in patients who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.
Route of Administration	Oral
Dosage Form	Tablet
Strength	15 mg/6.14 mg and 20 mg/8.19 mg
Dose and Frequency	The recommended starting dose of Lonsurf (b) (4) is 35 mg/m2/dose (b) (4) orally twice daily (b) (4) (b) (4) (b) (4) (b) (4)
How Supplied/ Container Closure	HDPE bottles with child resistant closures containing 20, 40, or 60 tablets each.
Storage	Store at 20° to 25°C (68° to 77°F); excursions are permitted from 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Lonsurf labels and labeling submitted by Taiho.

- Container label (submitted May 20, 2015)
- Carton labeling (submitted May 20, 2015)
- Prescribing Information (submitted February 19, 2015 and May 20, 2015)

G.2 Label and Labeling Images

Container Labels

(b) (4)

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OTTO L TOWNSEND
06/17/2015

CHI-MING TU
06/17/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

NDA Number: 207,981

Sponsor: Taiho Oncology, Inc

Drug, Formulation: Lonsurf (Trifluridine/tipiracil hydrochloride), tablet

Indication: Metastatic colorectal cancer in patients previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy

Proposed Pediatric Regimen: None

Memo: The Division of Oncology Products 2 (DOP2) requested DPMH input on a Pediatric Research Equity Act (PREA) waiver request for all pediatric populations from birth, as well as a Maternal Health labeling review.

DOP2 previously agreed to a waiver of pediatric studies (iPSP Agreement Letter, IND 57674, June 10, 2014). Per discussions with the DOP2 medical officer team leader (MO-TL, Lemery, S., MD; January 28, 2015), DOP2 continues to believe that pediatric studies are impracticable because colorectal cancer (including metastatic disease) is rare in the pediatric population. This reviewer identified references for incidence of pediatric colorectal cancer (of any cell type) of approximately 1 per million in the United States (159 pediatric cases; reported ages 4 to 20 years, from 1973 through 2005).[1]

DPMH agrees that pediatric studies under PREA are impracticable and should be waived. Additionally, while searches of PubMed, DARRTS, and clinicaltrials.gov performed for this review found no other likely conditions for study in children, DPMH defers rendering an opinion on issuance of a pediatric WR since the MO-TL recommended wider discussion, possibly including opinions from the Oncology Drug Advisory Committee (ODAC).

The Maternal Health labeling review will be performed separately (pending).

[1] Sultan I, Rodriquez-Galindo C, El-Taani H, et al. Distinct features of colorectal cancer in children and adolescents. A population-based study of 159 cases. Cancer. 2010 Feb 1;116(3):758-65.

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ETHAN D HAUSMAN
05/26/2015