CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10 Sep 2015
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	207981
Applicant	Taiho Oncology, Inc. (Taiho)
Date of Submission	19 Dec 2014
PDUFA Goal Date	19 Dec 2015
Proprietary Name / Established Name	Lonsurf / trifluridine - tipiracil hydrochloride
Dosing Regimen	35 mg/m^2 orally twice daily for five consecutive days a week for two weeks followed by a 14 day rest
Proposed Indication(s)	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.
Recommended:	*Approval contingent upon final agreement upon labeling and post marketing commitments/requirements.*

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1. Introduction

FDA received the complete New Drug Application (NDA) 207981 from Taiho Oncology, Inc. (Taiho) on 19 Dec 2014 requesting marketing authorization (regular approval) for TAS-102 (trifluridine/tipiracil hydrochloride, proposed trade-name Lonsurf) 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 application was received as a rolling submission. The first unit (nonclinical unit) was submitted on 16 Oct 2014.

Disclaimer: Any data or information described below that Taiho does not own (for example, summary data from other drugs used to treat patients with metastatic colorectal cancer or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The primary issues considered during the review of this NDA for TAS-102 were whether the trials submitted to the application constitute substantial evidence of effectiveness; whether the risk-benefit profile of Lonsurf is favorable for the intended indication; and whether both trifluridine and tipiracil are necessary to achieve the intended effect. This section of the review will highlight the primary issues related to this NDA; however, to avoid redundancy, the risk-benefit discussion will be found at the end of this review.

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) states that reliance on a single adequate and well controlled study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and confirmation of the results in a second trial would be practically or ethically impossible.

The submission of this application was primarily based on the results of one study entitled "Randomized, 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 Therapies" [TPU-TAS-102-301 (301) also known as RECOURSE].

Study 301 (Refer to Section 7 of this review for details of the trial) appeared to be a well conducted, adequate and well controlled trial that demonstrated a survival advantage following treatment with TAS-102 as compared to placebo. The survival effect in Study 301 (summarized in Table 1), a large multi-center and international trial, was statistically robust and supported by a statistically robust (although clinically modest) effect on progression free survival. This reviewer would expect such findings to be replicated if a second study were conducted.

Table 1 Summary of OS efficacy results, Study 301

	TAS-102 N = 534	Placebo N = 266
# of events	364	210
Median (in mos.)	7.1	5.3
Stratified HR (95% CI)	0.68 (0.58, 0.81)	
p-value (two-sided)	< 0.001	

Although this application was primarily based on the results of one trial, Taiho submitted the results of a second randomized trial conducted solely in Japan (Study J003-10040030). Study J003-10040030 randomized 172 patients with mCRC to receive either TAS-102 or placebo. Although the trial was not designed with a two sided alpha of 0.05, the study demonstrated improved survival among TAS-102-treated patients. Median OS was 9 months in the TAS-102 arm compared to 6.6 months in the placebo arm (HR = 0.56; p = 0.0011). Although smaller and conducted in a single country, this study appears to provide strong supportive evidence regarding the reliability of the survival effect observed in Study 301.

Based on the results of Study 301 supported by the results of Study J003-10040030, this reviewer agrees that this application contained substantial evidence that TAS-102 can prolong survival when administered to patients with previously treated, metastatic colorectal cancer.

TAS-102 contains two drugs, trifluridine and tipiracil hydrochloride. Trifluridine or FTD is the anti-neoplastic moiety and is a thymidine-based nucleoside analogue. Tipiracil or TPI does not inhibit tumor growth; however, TPI altered the exposure of FTD in multiple *in vivo* studies through inhibition of thymidine phosphorylase. Although TPI does not have anti-cancer effects, it does increase the exposure of FTD to levels that can induce a therapeutic effect.

Taiho conducted Study TPU-TAS-102-102 to evaluate the contribution of TPI to TAS-102. This study evaluated the pharmacokinetics of a single dose of FTD as a component of TAS-102 compared to the pharmacokinetics of a single dose of FTD alone. FTD plasma concentrations ($AUC_{0\text{-last}}$) were approximately 37-fold higher when administered as a component of TAS-102 compared to FTD alone. Taiho extrapolated that based on AUC values, that an FTD dose of 1295 mg/m^2 would be required to achieve similar concentrations of FTD when administered as a component of TAS-102. This 1295 mg/m^2 dose is higher than the dose of FTD that Taiho predicted would exceed the lethal dose for humans (1194 mg/m^2) based on primate toxicology studies.

Based on these data, and based on the improvement in overall survival observed in Study 301, this reviewer agrees that the product should be approved as a combination product (as opposed to an approval based on FTD-alone).

2. Background

2.1 Disease and therapy related issues

Taiho requested marketing authorization for TAS-102 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. In general, because metastatic colorectal cancer is an incurable disease (with the exception of certain patients with oligometastatic disease), the goal of treatment for these patients is to prolong life and/or improve quality of life.

2.2 U.S. regulatory history

The following summarizes the pertinent regulatory history and meetings held in relation to this NDA. Meetings held to discuss clinical trials pertinent to other indications were not summarized in this review. Although not necessarily pertinent to the U.S. regulatory history, Japan approved TAS-102 on 24 Mar 2014 for the treatment of patients with unresectable advanced or recurrent colorectal cancer. Taiho stated that the approval was primarily based on the results of a randomized double-blind, placebo controlled, clinical trial conducted in Japan (J003-10040030). The trial was designed with a one-sided Type 1 error rate of 0.1 with overall survival as the primary endpoint.

29 Nov 2011 (Type B, Chemistry, Manufacturing and Controls meeting): FDA and Taiho held this meeting to discuss future development of the manufacturing of the drug substance (DS) and drug product (DP) to support a New Drug Application for TAS-102. During the meeting, Taiho described plans to register (b) (4) Taiho proposed to conduct a two-week repeat dose toxicity study in rats in order to evaluate the safety of FTD manufactured at (b) (4) (b) (4).

During the meeting, FDA recommended that Taiho designate one primary manufacturing site for DS (with the other site designated as the alternate site). FDA stated that the NDA should contain stability data from product manufactured at both sites. FDA also stated that the proposed non-clinical toxicology bridging study appeared acceptable pending review of the study under the IND.

FDA agreed with the proposal to designate (b) (4) as starting materials; however, FDA provided recommendations regarding critical quality attributes and impurities.

FDA recommended one single drug substance specification regardless of drug source; however, FDA agreed with a proposal to include (b) (4) impurity methods in the DS specification.

Regarding starting materials for TPI, FDA agreed with the designation of (b) (4) as a starting material; however FDA requested additional information regarding the acceptance of (b) (4) as a starting material.

FDA also agreed that Taiho can use draft USP specification for limits for metals (b) (4) .

12 Dec 2012 (Type B, End-of-Phase 2 meeting): FDA and Taiho held this meeting to discuss the design of TPU-TAS-102-301 intended as an adequate and well controlled study in order to support approval of TAS-102 as a treatment for patients with metastatic colorectal cancer. Although the IND was previously inactivated, Taiho reinitiated development of TAS-102 based on the results of a randomized trial conducted solely in Japan that investigated the dose of 35 mg/m^2 administered twice daily. The following items were discussed during the meeting or described in the meeting minutes.

- FDA recommended that Taiho investigate whether the proposed 35 mg/m^2 twice daily dose was reasonably safe in the U.S. population prior to initiating the proposed pivotal trial. A previous study conducted in a (more) heavily treated breast cancer population established 25 mg/m^2 twice daily as the maximum tolerated dose. Taiho agreed to not initiate TPU-TAS-102-301 until at least 18 evaluable patients completed at least one cycle of investigational treatment and determined the proposed dose to be reasonably safe.
- Taiho would need to provide justification in an NDA that the results of the study are applicable to the U.S. population.
- Taiho would need to provide justification in an NDA that TPI is a necessary component of TAS-102 and why FTD alone (e.g., at a higher dose or more frequent schedule) is not sufficient to provide the proposed treatment effect. FDA agreed that the general design of a proposed PK study may be able to characterize the pharmacokinetics of FTD with and without TPI.
- FDA provided advice regarding the need to evaluate QT/QTc in support of a marketing application.
- FDA provided advice regarding the statistical analysis plan for the proposed protocol including pre-specification of the number of events for the final analysis and to control for multiplicity for testing of secondary endpoints. Taiho stated that PFS will be the only key secondary endpoint for registration purposes.
- FDA asked Taiho to provide justification and data to support the administration of TAS-102 under fed conditions in the ongoing and proposed clinical trials. Taiho provided summary data from an animal study and stated that TAS-102 has been administered in the fed state in clinical trials. Taiho stated that a food effect study was ongoing and was to be completed prior to the initiation of the proposed randomized controlled trial (TPU-TAS-102-301).

15 May 2012 (letter to Taiho): FDA sent Taiho a letter following the review of a 12 Apr 2012 amendment to the IND. FDA stated that based on data from the food effect trial, that TAS-102 should be administered under the same fed conditions (e.g., within 1 hour after completion of morning and evening meals) as specified in previous TAS-102 clinical trials.

07 Jan 2013 (email to Taiho): FDA notified Taiho that the Agency found the design of Study TPU-TAS-102-102 entitled, “Phase 1, Open-Label, Randomized, Parallel Group Study

Evaluating the Pharmacokinetics of FTD as a Component of TAS 102 Compared with FTD Alone" acceptable from a clinical pharmacology perspective.

14 Jan 2013 (letter to Taiho): FDA provided advice regarding a protocol entitled, "A Phase 1 Study to Evaluate the Cardiac Safety of Orally Administered TAS-102 in Patients with Advanced Solid Tumors."

26 Mar 2014 (email to Taiho): FDA stated that the design of Protocol TAS-102-104 was acceptable to fulfill clinical pharmacology bioavailability requirements.

25 Oct 2013 (letter to Taiho): FDA (DMEPA) sent Taiho a letter that the proposed proprietary name, Lonsurf, was acceptable; however, FDA asked Taiho to submit a new request for proprietary name review upon submission of the NDA.

27 Nov 2013 (preliminary meeting comments for a planned 5 Dec 2013 Type B, pre-NDA, CMC meeting): Taiho requested this meeting in order to prepare CMC sections of a future NDA and to follow up on items discussed during the CMC meeting held on 29 Nov 2011. Following review of FDA comments, Taiho elected to cancel the meeting as further discussion was not needed. The following items/responses were contained within the document:

- Taiho's approach to the submission of stability data was acceptable and that Taiho could provide 12 month stability data within 30 days after the NDA submission.
- FDA agreed with the proposed approach to place one batch of each product strength packaged in the commercial container closure system on an annual stability program post approval.
- FDA concurred with the strategy to include executed batch records for bulk tablets of a full production scale lot of each strength of TAS-102 in the regional section of the NDA at submission.
- FDA agreed with Taiho's proposal regarding freeze/thaw studies.
- FDA stated that proposed acceptance criteria for related substances in (b) (4) and specifications for (b) (4), a starting material in TPI DS, appeared acceptable; however, final determination would be made during review of the relevant information in the NDA.

31 Jul 2014 (Type B pre-NDA meeting): Taiho requested this meeting to discuss and reach agreement on the contents and format of the proposed NDA for TAS-102. FDA recommended that Taiho request Fast Track status in order to allow for the submission of a rolling NDA and submit, if ready and complete, toxicology/non-clinical sections of the NDA prior to submission of other major components of the complete NDA. The following items were discussed during the meeting or described in the meeting minutes.

- Agreement was reached on the submission of non-clinical components of the application.
- FDA agreed that the clinical trial package appeared adequate to support the review of an NDA and stated that the application would be subject to a filing review to assess the completeness of the application.

- FDA agreed with Taiho's plan to not submit a pooled efficacy analysis of studies J003-10040030 and TPU-TAS-102-301.
- Agreement was reached on the datasets to be submitted in the integrated summary of safety.
- FDA agreed to the proposed data cutoff date of 24 Jul 2014 provided that the NDA was submitted on the planned date in mid-December 2014.
- FDA and Taiho discussed considerations for priority review and the safety update. FDA requested that Taiho limit new safety information in the update to safety information that would reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in product labeling. Taiho stated that 18% of randomized patients received prior regorafenib and that the treatment effect of TAS-102 was the same in this subgroup. FDA stated that Taiho's proposed approach to support priority review status was acceptable; however, agreement was not reached on granting of priority review.
- FDA agreed with Taiho's approach to submit financial disclosure information from studies J003-10040030 and TPU-TAS-102-301.
- FDA agreed that based on preliminary evaluation of the data provided in the briefing package, that a REMS did not appear necessary for filing.
- FDA provided comments regarding the proposed label.
- FDA requested that, in the NDA, Taiho provide adequate justification that TPI is a necessary component of TAS-102 and why trifluridine alone is not sufficient to provide the proposed treatment effect. In addition to providing pharmacokinetic data to support this justification, FDA recommended that Taiho provide a discussion regarding the practicality (or lack thereof) if a patient were required to take trifluridine alone (without TPI).
- Ultimately, FDA and Taiho reached agreement on the content and format of all modules of the NDA. Taiho would submit OSI-requested datasets to the IND or NDA prior to the submission of the last module of the NDA. FDA and Taiho agreed that the 5 Dec 2013 preliminary comments from FDA ONDQA stood as the final pre-NDA CMC meeting minutes.

2.3 Application history

The following table summarizes the contents of amendments submitted to the NDA.

Table 2 Amendments to NDA 207981 (as of the date of the completion of this review)

Date of Submission	Purpose of Submission
16 Oct 2014	Submission of Module 4 of the NDA (and related sections in Modules 1 and 2).
07 Nov 2014	Submission of the second reviewable unit of the NDA. This submission included datasets requested by the Office of Scientific Investigations.
19 Dec 2014	Submission of the remaining components of the NDA under the rolling submission.
22 Dec 2014	Request for a proprietary name review for the proprietary name Lonsurf.
05 Jan 2015	Taiho provided the addresses and contact information for the sites containing TPU-TAS-102-301 study master files.

Date of Submission	Purpose of Submission
06 Jan 2015	Taiho provided an updated Form 356(h) with all manufacturing, packaging, and inspection information. Taiho also provided a formal request for waiver of the PREA requirements (disease-specific request).
16 Jan 2015	Submission of 12 month drug product stability data for all three primary stability batches of each of the tablet strengths.
26 Jan 2015	Taiho provided a letter agreeing to provide the risk management plan to FDA (based on a DRISK request) at the same time that they submit the plan to the EU.
3 Feb 2015	Taiho formally provided Applicant orientation materials that were used during the 2 Feb 2015 Applicant Orientation Meeting.
12 Feb 2015	Taiho sent a letter notifying FDA that they would submit a Pharmacovigilance Plan in accordance with the E2E Pharmacovigilance Planning Guidance for Industry and submit the document to the NDA during the week of 9 Mar 2015.
13 Feb 2015	Taiho provided information in response to a CMC information request.
18 Feb 2015	Taiho provided the DMC minutes from Study TPU-TAS-102-301.
19 Feb 2015	Taiho provided a revised draft label in response to FDA recommendations sent to Taiho (dated 5 Feb 2015).
27 Feb 2015	Taiho submitted their proposed EU risk management plan.
03 Mar 2015	Taiho submitted updated SDTM define files for all eight TAS-102 studies based on an FDA request during a 2 Feb 2015 meeting.
06 Mar 2015	Taiho provided data intended to assist the Agency in populating tables to be included in the FDA Drug Trials Snapshot Website.
06 Mar 2015	Taiho provided a response to an FDA information request regarding the difference in the number of on-treatment deaths (by two patients) in the different datasets and the CSR narratives.
09 Mar 2015	Submission of a PK/PD analysis report and datasets for exposure-response analyses.
13 Mar 2015	Submission of additional details in regards to financial disclosure information following FDA requests dated 26 Jan 2015 and 5 Mar 2015.
16 Mar 2015	Submission of US Pharmacovigilance Plan in accordance with E2E (Pharmacovigilance Planning Guidance for Industry).
19 Mar 2015	Submission of the 90-day Safety Update Report.
17 Apr 2015	Amendment that further defined the variable "RECADY" in the ADLB dataset.
12 May 2015	Taiho provided clarification regarding how certain safety analyses were performed.
20 May 2015	Submission of revised carton and container labeling.
28 May 2015	Submission of additional PK information regarding clearance from Study 12DA25 (based on an FDA information request dated 16 May 2015).
28 May 2015	Notification of a change in contact for Taiho Oncology, Inc.
3 Jun 2015	Submission of all Study 301 protocol amendments using track-change features.
3 Jun 2015	Response to FDA information request dated 4 May 2015 regarding CMC information.
5 Jun 2015	Submission of additional PK information from patients with renal impairment from Study 301 (based on an FDA information request dated 16 May 2015).
9 Jun 2015	Submission of the original 301 protocol.
17 Jun 2015	Re-submission of draft label in SPL format in response to FDA email request dated 12 Jun 2015.

Date of Submission	Purpose of Submission
13 Jul 2015	Taiho provided information regarding the potential concomitant use of TAS-102 with thymidine kinase substrates such as certain antiviral drugs.
24 Jul 2015	Taiho provided a response to a CMC information request.
31 Aug 2015	Submission of revised labeling.
8 Sep 2015	Submission of revised carton and container labeling.

3. CMC

The joint quality review authored by Dr.'s Erika Englund (drug substance), Rajiv Agarwal (drug product), Quamrul Majumder (process and microbiology), Marisa Heayn (facility), Salaheldin Hamed (biopharmaceutics), Rabiya Laiq (project/business manager), Olen Stephens (application technical lead), Mike Trehy (laboratory), and Sharon Thoma (ORA lead) recommended approval of NDA 207981. Quality reviewers found the manufacturing and testing facilities for this NDA to be acceptable.

3.1 Drug substance

TAS-102 (trifluridine/tipiracil hydrochloride) is a fixed drug combination (1:0.5) product containing α,α,α-trifluorothymidine (FTD) and 2,4 (1H,3H)-pyrimidinedione, 5-chloro-6-[2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (TPI). As per the DS review, per the salt nomenclature policy, the established name for TPI only captures the base and not the salt form.

The DS review stated that both drug substances are highly soluble and that absorption is expected to be determined by the permeability of the two drug substances.

3.2 Drug product

Two different tablet strengths exist. One tablet contains 15 mg of trifluridine and 6.14 mg of tipiracil. These tablets are white, round, biconvex, immediate-release film-coated tablets. The second tablet contains 20 mg trifluridine and 8.2 mg tipiracil. The 20 mg/8.2 mg tablets are pale red, round, biconvex, immediate-release film-coated tablets. Each strength will be available in 20, 40, and 60 tablet count bottles. The DP review stated that the compendial excipients used in the formulation comply with requirements of the compendial references listed.

The quality review stated that 24 months of expiration data may be granted for this product based on the totality-of-stability data at 12 months at long term storage conditions and six months at accelerated storage conditions.

3.3 Facilities

All manufacturing sites for DS and DP were determined to be acceptable. FTD DS is manufactured via chemical synthesis (b) (4) (b) (4) TPI DS is manufactured via chemical synthesis by Taiho Pharmaceutical Co., Ltd., at 200-22, Motohara, Kamikawa-machi, Kodama-gun, Saitama, Japan. TAS-102 DP is manufactured at Taiho Phamaceutical Co., Ltd., at 1-1 Iuchi, Takabo, in Tokushima, Japan. Refer to the Quality review for names and locations of testing and packaging sites.

4. Nonclinical Pharmacology/Toxicology

Drs. G. Sachia Khasar and Emily Wearne, the primary nonclinical reviewers, concluded that the nonclinical studies were sufficient to support the use of TAS-102 in the proposed patient population and that there were no outstanding nonclinical pharmacology/toxicology issues preventing the approval of TAS-102.

4.1 Nonclinical pharmacology

TAS-102 is a combination product consisting of trifluridine (FTD) and tipiracil in a fixed 1:0.5 ratio. FTD is the anti-neoplastic moiety and is a thymidine-based nucleoside analogue. As described in the proposed product label, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. This statement was supported by the results of pharmacology studies described in the non-clinical reviews.

TPI does not inhibit tumor growth; however, TPI altered the exposure of FTD in multiple *in vivo* studies through inhibition of thymidine phosphorylase.

4.2 Nonclinical toxicology

As summarized in Dr. Helms's supervisory review, the major targets of FTD:TPI in rat and monkey toxicology studies were the bone marrow and gastrointestinal tract. These toxicities predicted the most frequent and severe clinical toxicities observed to date in humans.

The following additional items were highlighted in the toxicology reviews:

- Both FTD and TPI were present in the milk of lactating rats following exposure to FTD and TPI.
- Rats exposed to FTD and TPI experienced dental changes including whitening, breakage, and malocclusion. This information was recommended for inclusion in Section 8.4 of the product label.
- FTD caused genotoxicity in *in vitro* genotoxicity assays. Structural anomalies including kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies were observed in rat studies. TPI alone was negative in the genotoxicity assays. Based on these findings, the label will contain a warning for embryofetal risk.
- FTD:TPI resulted in increased post-implantation loss in female rats.

5. Clinical Pharmacology

5.1 General clinical pharmacology considerations

The clinical pharmacology review team [Dr. Xianhua (Walt) Cao (DCPV) and Dr. Jingyu (Jerry) Yu] concluded that this NDA is acceptable from a clinical pharmacology perspective. OCP recommended two PMRs to complete ongoing studies intended to determine the appropriate dose of TAS-102 in patients with hepatic and renal impairment.

5.1.1 Dose selection

The applicant evaluated the tolerability of TAS-102 in a dose-finding study conducted in Japan. Confirmation of tolerability of the 35 mg/m^2 twice daily dose (based on the trifluridine

component) in Western patients was based on an additional dose finding study in the U.S. (TPU-TAS-102-101). In Study TPU-TAS-102-101, the applicant reported one of nine patients in the 35 mg/m^2 cohort as experiencing a dose limiting toxicity (Grade 3 febrile neutropenia).

Taiho also conducted Study TPU-TAS-102-102 to evaluate the contribution of TPI to TAS-102. This study evaluated the pharmacokinetics of a single dose of FTD as a component of TAS-102 compared to the pharmacokinetics of a single dose of FTD alone. All patients could subsequently receive TAS-102 in an extension part of the study. Table 8 and Figure 3 in the Clinical Pharmacology Review (both copied from the NDA submission) show that FTD plasma concentrations ($AUC_{0\text{-last}}$) were approximately 37-fold higher when administered as TAS-102 compared to FTD alone.

Taiho extrapolated that based on AUC values, that an FTD dose of 1295 mg/m^2 would be required to achieve similar concentrations of FTD when administered as a component of TAS-102. This dose is higher than the dose of FTD that Taiho predicted would exceed the lethal dose for humans (1194 mg/m^2) based on primate toxicology studies. Furthermore, the addition of tipiracil reduced the variability of FTD C_{max} (C_{max} appears associated with neutropenia).

Comment: Based on these data, and based on the improvement in overall survival observed in Study 301, this reviewer agrees that the product should be approved as a combination product (as opposed to an approval based on FTD-alone).

5.1.2 Pharmacokinetics

After a single 35 mg/m^2 dose (based on trifluridine content), mean elimination half-life of trifluridine was 1.4 hours and of tipiracil was 2.1 hours. At steady state, the mean elimination half-life was 1.2 hours for trifluridine and 2.4 hours for tipiracil. As described in Section 5.1.1 above, tipiracil increased the mean $AUC_{0\text{-last}}$ of FTD by 37-fold. Tipiracil also increased C_{max} of FTD by 22 fold with reduced variability in FTD C_{max}.

A standardized high-fat, high calorie meal decreased the C_{max} of trifluridine and the C_{max} and AUC of tipiricil; however, the high-fat meal did not change the AUC of trifluridine. OCP recommended that patients take Lonsurf within one hour after completion of the morning and evening meals because C_{max} appeared to correlate with decreased neutrophil counts.

5.2 Drug-drug interactions

The OCP review stated that trifluridine is a substrate of thymidine phosphorylase and not metabolized by cytochrome P450 enzymes. Additionally, trifluridine and tipiracil did not inhibit or induce CYP1A2, CYP2B6, or CYP3A4/5. Although the OCP review stated that tipiracil was a substrate and an inhibitor of OCT2 *in vitro* at C_{max} concentrations 3 fold higher than observed in clinical studies, the population PK analysis suggested that concomitant OCT2 inhibitors did not alter the pharmacokinetic parameters of trifluridine or tipiracil.

5.3 Demographic interactions/special populations

The clinical pharmacology review stated that body size and renal function were the primary intrinsic factors affecting exposure of FTD and TPI in a population pharmacokinetic analysis of data from 239 patients. The data were insufficient to accurately characterize E-R

relationships of TAS-102 based on Study 301. The OCP review stated that other covariates tested including age, sex, and mild hepatic impairment had no clinically meaningful impact on exposure to trifluridine or tipiracil.

5.4 Thorough QT study or other QT assessment

The OCP review stated that TAS-102 was administered to 42 patients with advanced solid tumors at the recommended dose and that this dose did not result in a large effect on mean QTc intervals when compared to placebo. The review also stated that there was no evidence of an exposure/QT relationship.

6. Clinical Microbiology

This section is not applicable to this review.

7. Clinical/Statistical-Efficacy

The statistical reviewer [Dr. Weishi (Vivian) Yuan] concluded that based on the data and analyses from Study 301, TAS-102 demonstrated a statistically significant improvement in OS compared to placebo. The clinical reviewer (Dr. Leigh Marcus) recommended approval of this application based on the improvement in overall survival demonstrated in Study 301 and based on the favorable risk-benefit profile.

This section of the CDTL review will focus on the demonstration of safety and efficacy in the pivotal adequate and well controlled trial (Study 301) and thus will not focus on trials in other indications (e.g., that provided safety data) or on trials that supported the dose of TAS-102 (refer to Clinical Pharmacology Section above).

7.1 Background of clinical program

The protocol for the pivotal trial [301 (TPU-TAS-102-301) also known as RECOURSE] was dated 23 Feb 2012 and contained the following title: Randomized, 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 Therapies.

Study 301 was amended globally three times; however, the first two amendments were dated (28 Mar 2012 and 22 Apr 2012) prior to the enrollment of the first patient on 17 Jun 2012. The third amendment, dated 13 Nov 2012, clarified the timing of certain end-of-treatment assessments; modified an exclusion criterion regarding unresolved toxicities associated with prior therapies; and clarified procedures in case the study blind needed to be broken.

Additional country-specific amendments were made; however, these amendments were minor and would not have affected the overall conclusions of the study.

In addition to the pivotal 301 trial, Taiho submitted the results of a supportive randomized trial conducted in Japan (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.”

7.2 Design of 301

7.2.1 Primary endpoint (301)

The primary endpoint of 301 was overall survival (OS), defined as the time from randomization to the date of death from any cause. *Comment: As stated in the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf; accessed on 21 Apr 2015), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.*

7.2.2 Secondary endpoints (301)

Secondary endpoints defined by the original protocol included progression free survival (PFS), time to treatment failure, overall response rate, disease control rate, and duration of response. The protocol indicated that PFS was the only key secondary endpoint for registration purposes and therefore, no further multiplicity adjustments were made.

The protocol defined PFS as the time from the date of randomization until the date of investigator-assessed radiological disease progression or death due to any cause (refer to biometrics review for censoring rules and methodology of sensitivity analyses).

Although not a key secondary endpoint, the protocol defined ORR as the proportion of patients with objective evidence of complete response (CR) or partial response (PR).

The use of investigator assessments for progression (and response) was acceptable because the primary endpoint was overall survival (i.e., the PFS and ORR endpoints are considered supportive of the overall survival results).

7.2.3 Eligibility criteria (301)

The study enrolled patients older than 18 years of age with metastatic colorectal cancer who had received at least two prior regimens in the metastatic setting. Patients must have received all of the following agents approved in each country: fluoropyrimidines, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody, and at least one anti-EGFR monoclonal antibody (if the patient's tumor was KRAS wild type).

The protocol also listed the following additional eligibility criteria (*for brevity, only select criteria are listed*): ECOG 0-1; absolute neutrophil count ≥ 1,500/mcL; platelet count > 100,000/mcL; total bilirubin ≤ 1.5 mg/dL (except Grade 1 hyperbilirubinemia due solely to Gilbert's syndrome); AST or ALT ≤ 3 times the upper limit of normal (or ≤ 5 times if due to liver metastasis); and serum creatinine ≤ 1.5 mg/dL.

The protocol excluded patients with the following (*for brevity, only select criteria are listed*): brain or leptominigeal metastasis; ascities, pleural effusion, or pericardial effusion requiring drainage in the last four weeks; uncontrolled diabetes; GI hemorrhage; HIV infection; pregnancy; and with certain unresolved toxicites attributed to prior therapies.

7.2.4 General study design/treatment plan (301)

- The trial was a double-blinded, randomized (2:1), multi-center, international trial. Randomization occurred centrally via an Interactive Voice/Web Response System using a dynamic allocation method (biased coin).
- Study 301 randomized patients to receive either placebo or TAS-102 twice daily at a dose of 35 mg/m^2/dose. In each 28 day cycle, patients received TAS-102 or placebo twice daily for five days with two days' rest for two weeks, followed by a two week rest period.
- Patients underwent a CT scan of the chest and abdomen (and pelvis if clinically indicated) every eight weeks until disease progression.
- The protocol contained a monitoring plan that obtained hematology and chemistry labs at baseline and on days 1 and 15 of subsequent cycles. ECGs were obtained at baseline and on days 1 and 12 of Cycle 1. Investigators performed a physical exam at baseline and on day 1 of each cycle.
- The protocol contained instructions for the management of non-hematologic toxicities that required interruption of treatment for ≥ Grade 3 treatment-related toxicities except for Grade 3 nausea, vomiting, or diarrhea [and certain other non-serious events unlikely to become serious at the discretion of the investigator (e.g., fatigue or changes in libido)]. Following dose interruption for ≥ Grade 3 adverse events, the dose was reduced at the time of the next cycle (the dose levels were 35 mg/m^2, 30 mg/m^2, 25 mg m^2, and 20 mg/m^2).
- The protocol required TAS-102 or placebo to be held for neutrophils < 500/mcL until recovery to ≥ 1,500/mcL or platelets < 50,000/mcL until recovery to ≥ 75,000/mcL. Patients who experienced febrile neutropenia or uncomplicated Grade 4 neutropenia or thrombocytopenia that delayed the initiation of the next cycle by greater than one week would start the next cycle at a reduced dose.
- Patients continued either blinded placebo or TAS-102 until progressive disease, unacceptable toxicity, pregnancy, physician decision, or withdrawal of consent.
- The protocol established an independent Data Monitoring Committee (DMC) to periodically assess safety data.

7.2.5 Statistical design and analysis issues (301)

Randomization/Stratification Factors

The protocol specified the following stratification factors: KRAS gene type (wild, mutant); time since diagnosis of metastasis (< 18 months, ≥ 18 months); and geographical region [Region 1: Asia (Japan); Region 2: Western (US and Europe)].

Determination of Sample Size

The protocol stated that 800 patients were to be randomized (2:1) to each arm. A total of 571 events (deaths) were required for 90% power to identify an improvement in OS at a HR of 0.75 (estimated OS of 5 months in the placebo arm) at a 0.05 two-sided significance level. There were no planned interim analyses because of anticipated rapid enrollment.

Analyses
The protocol stated that the primary efficacy analysis for overall survival would be tested using a stratified log-rank test. The protocol specified that the primary analysis would be conducted using the intent-to-treat population consisting of all patients randomized.

7.3 Design of J003-10040030

J003-10040030 was a multicenter, double-blind, randomized (2:1) trial conducted in Japan. The trial evaluated and compared overall survival in patients with metastatic colorectal cancer who received TAS-102 versus placebo (same dose and schedule as Study 301). Enrollment criteria differed from Study 301 as prior treatment with an EGFR inhibitor or VEGF inhibitor was not required and the study enrolled patients ≥ 20 years of age. Study J003-10040030 also allowed patients to be enrolled with ECOG 0 to 2.

Study J003-10040030 was designed with 80% power and a one-sided 10% significance level. The estimated median survival times were set at 9 months for the TAS-102 arm versus 6 months for placebo. The study targeted a total randomized patient count of 162 assuming a registration period of 12 months and a follow-up period of 12 months. The protocol indicated that the expected number of events at the 12-month survival follow-up period would be 121. The period when the anticipated number of events was reached was designated as the implementation period for the primary analysis.

7.4 Efficacy results (Study 301)

The first patient was randomized into Study 301 on 17 Jun 2012 and the last patient was randomized on 08 Oct 2013. A total of 1002 patients provided consent, and 202 patients were not randomized (with the majority related to ineligibility for one or more of the exclusion criteria). The study data cut-off date for overall survival was 24 Jan 2014 and the study data cut-off date for all data except overall survival was 31 Jan 2014. One patient in the TAS-102 arm did not receive treatment and one patient in the placebo arm did not receive placebo.

7.4.1 Demographics (Study 301)

Median age of patients randomized in both arms was 63 years. Japan was the country that enrolled the highest percentage of patients (33%) and more men were enrolled than women. Black patients were under-represented as compared to the U.S. population. Table 3 (data from Dr. Marcus's review) shows that the gender and ethnic background of patients enrolled into Study 301 were similar between arms.

Table 3 Demographics, Study 301

	TAS-102 N=534 (%)	Placebo N=266 (%)
Age		
≥ 65 years	44	44
Female		
Yes	39	38
Race		
White	57	58
Black	1	2

	TAS-102 N=534 (%)	Placebo N=266 (%)
Asian	34	35
Not-collected	7	5
Geographic Region		
Asia (Japan)	33	33
US, EU, Australia	67	67

In general, disease characteristics of patients were balanced across the two arms. Although minor differences existed across arms in certain specific sites of metastasis, the number of organ sites involved (median = 2 in both arms) and number of metastatic lesions (median = 4 in both arms) were balanced. All patients received prior treatment with a fluoropyrimidine, irinotecan, and oxaliplatin. All but one patient in the placebo arm received prior bevacizumab. All but one patient with KRAS wild-type CRC in each arm received prior cetuximab or panitumumab. Across both arms, 18% of patients received prior regorafenib.

Table 4 shows disease characteristics at baseline. BRAF status was not available from most patients (85%) across both arms in Study 301.

Table 4 Disease characteristics at baseline, Study 301

	TAS-102 N=533 (%)	Placebo N=266 (%)
ECOG PS		
0	56	55
1	44	45
Location		
Colon	63	61
Rectum	37	39
KRAS Status		
Wild-type	49	49
Mutant	51	51
Common sites of metastasis		
Liver	75	71
Peritoneum/malignant ascities	17	18
Lung	73	81
Bone	7	8

7.4.2 Disposition (Study 301)

All but one patient in each arm received study-directed investigational drugs. Therefore, the ITT population consisted of 800 patients and the safety evaluable population consisted of 798 patients. Table 5 (data rounded from Dr. Marcus's review) shows the reasons for discontinuation of TAS-102 or placebo during the trial. Most patients in both arms discontinued due to progressive disease; however, a higher proportion of patients discontinued due to progressive disease in the placebo arm. The number of patients in the TAS-102 arm in

Table 5 does not add up to 100% because 7% of patients remained on TAS-102 as of 31 Jan 2014 (compared to 0.8% on placebo).

Table 5 Patient disposition, Study 301

	TAS-102 N=534 (%)	Placebo N=266 (%)
Progressive disease	84	95
Death	1	2
Withdrawal of consent	2	< 1
Adverse event	4	2
Other reasons	2	0
Administrative	< 1	0

The investigators (and applicant) appeared to adequately follow patients for survival. Three patients in each arm were lost to follow-up and one patient refused to continue with the study in the TAS-102 arm. At the time of data cut-off, 69% of patients died in the TAS-102 arm compared to 80% in the placebo arm.

7.4.3 OS analyses (Study 301)

Table 6, data obtained from the statistical review, shows the OS results determined at the time of data-cut off. Seventy-two percent of patients died (across both arms) by the time of data-cut off, constituting a mature analysis of survival. The pre-specified analysis of OS was statistically significant at the two-sided 0.05 level. The applicant and statistical reviewer conducted sensitivity analyses that supported the pre-specified findings.

Although the magnitude of the effect was clinically modest, i.e., a median difference of 1.8 months with a hazard ratio of 0.68, the effect was observed with a manageable toxicity profile, especially when compared to drugs commonly administered to patients with cancer.

Table 6 OS analyses (ITT), Study 301

	TAS-102 N=534	Placebo N=266
Number of deaths, n (%)	364 (69%)	210 (80%)
Median overall survival (months)	7.1	5.3
95% CI	(6.5, 7.8)	(4.6, 6.0)
HR (95% CI)	0.68 (0.58, 0.81)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

Figure 1, copied from the statistical and clinical reviews, shows the proportion of patients alive at each time point during the trial. The curves presented in the applicant's clinical study report were similar to the curves in the FDA reviews. Separation of the KM curves remained (approximately) constant throughout the duration of the trial.

Figure 1 KM curves for OS, Study 301

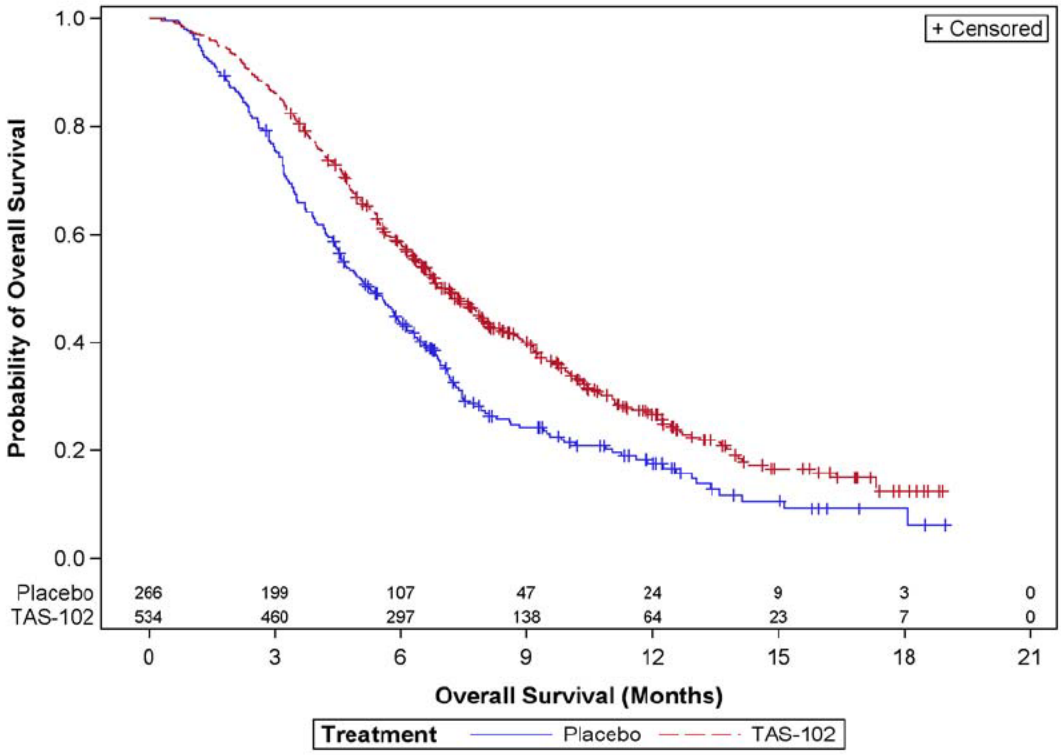

Table 7 (data copied from the statistical review) shows that for almost all subgroups tested (see statistical review for full list), that the HR (point estimate) was less than one. The upper bound of the 95% CIs for many of the subgroups was less than one, further supporting the statistical robustness of the overall results. The sample size in the subgroups where the 95% CI crossed one was smaller (than the overall patient population) and thus these subgroups were not adequately powered to demonstrate a (nominally) statistically significant effect on OS.

The HR for OS in the exploratory subgroup analysis of 99 patients enrolled in the U.S. (n = 64 for TAS-102 and 35 for placebo) was 0.56 (95% CI 0.34, 0.94). The HR (point estimate) in the exploratory subgroup of 144 patients who previously received regorafenib was 0.69 favoring the TAS-102 arm (95% CI 0.45, 1.05).

Table 7 Subgroup analyses for OS, Study 301

Subgroup	N*	HR (95% CI)
Race		
White	306/155	0.66 (0.52, 0.83)
Non-White%	228/111	0.71 (0.55, 0.92)
Gender		
Women	208/101	0.68 (0.51, 0.90)
Men	326/165	0.69 (0.55, 0.87)

Subgroup	N*	HR (95% CI)
Age in years		
< 65	300/148	0.74 (0.59, 0.94)
≥ 65	234/118	0.62 (0.48, 0.80)
Region		
Asia (Japan)	178/88	0.75 (0.57, 1.00)
US, EU, Australia	356/178	0.64 (0.52, 0.80)
Prior Therapy		
KRAS mutant	272/135	0.80 (0.63, 1.02)
KRAS wild-type	262/131	0.58 (0.45, 0.74)
Location of primary tumor		
Colon	338/161	0.68 (0.55, 0.85)
Rectal	196/105	0.64 (0.48, 0.85)
ECOG PS		
0	301/147	0.73 (0.57, 0.93)
≥ 1	233/119	0.61 (0.48, 0.79)

*TAS-102/placebo
% includes 52 patients for whom race was not collected

The point estimate for OS for one subgroup (patients who received two prior regimens) in the statistical review was greater than one (HR = 1.05); however, this subgroup was small and likely represented a chance finding. Furthermore, the hazards for survival across arms in this subgroup were not constant as the median OS was longer in the TAS-102 arm (and 25% of patients were still at risk at 10 months in this subgroup).

7.4.4 Secondary endpoints (Study 301)

The statistically designated secondary endpoint was progression free survival. Table 8 (data copied from the statistical review) shows that TAS-102 increased progression free survival compared to placebo. The effect at the median was modest (less than one month); however, the separation in the curves (see clinical and statistical reviews) increased after the medians such that the hazard ratio may be a better indicator of the treatment effect. *Comment: the lack of separation of the KM curves prior to the median was likely influenced by the imaging schedule.*

Table 8 PFS analyses (ITT), Study 301

	TAS-102 N=534	Placebo N=266
Number of events, n (%)	472 (88%)	251 (94%)
Median PFS (months)	2.0	1.7
95% CI	(1.9, 2.1)	(1.7, 1.8)
HR (95% CI)	0.47 (0.40, 0.55)	
Stratified log-rank test p-value[a]	< 0.0001	

[a] Stratified by planned stratification factors (see above)

Comment: Ultimately, the clinical benefit of TAS-102 is based on the effect on overall survival rather than the modest effect on PFS.

Few patients across both arms experienced an objective response. As described in the statistical review, 8 patients (1.5%) responded in the TAS-102 arm compared to one on placebo.

The applicant also conducted an analysis of time to ECOG performance status of ≥ 2. In the applicant's analysis, the median time to ECOG PS ≥ 2 was 4 months for placebo versus 5.7 months for TAS-102 [HR 0.66 (95% CI: 0.56, 0.78)]. Although the analysis was pre-specified in the protocol, alpha was not allocated for this analysis and therefore the results are considered exploratory. Additionally, the outcome was determined by physicians rather than patients; although the study was blinded, lab results likely resulted in unblinding of the assigned treatment arms. In summary, the ECOG PS results provided supportive evidence of benefit; however, the results (on worsening of ECOG PS) should not be considered as substantial evidence of effectiveness for purposes of product labeling.

7.5 Efficacy results (J003-10040030)

As previously described, J003-10040030 was a multicenter, randomized (2:1), double-blind study of TAS-102 conducted solely in Japan. The primary end-point was overall survival; however, because the applicant considered this as a phase 2 study, the primary analysis was conducted on the full analysis set (of all patients who received at least one dose of investigational drug and had at least one post-baseline efficacy assessment). The study was designed to detect a HR of 0.67 with 80% power and a one-sided alpha of 0.10. The cut-off date for the final analysis was 4 Feb 2011.

The following summarizes the applicant's analyses of supportive study J003-10040030. The study randomized 172 patients; of which the full analysis set consisted of 169 patients (112 for TAS-102 versus 57 for placebo). Median age was 63 years in the TAS-102 group compared to 62 for placebo. ECOG PS was 0 in 63% of patients and 1 in 34% of patients. Fifty four percent of patients were men. Median OS was 9 months in the TAS-102 group compared to 6.6 months in the placebo group [HR = 0.56 (95% CI: 0.39, 0.81)].

Although smaller and conducted in a single country, J003-10040030 appears to provide supportive evidence regarding the reliability of the survival effect observed in Study 301.

8. Safety

8.1 Adequacy of database

Based on the treatment effect (overall survival improvement) observed in Study 301, the clinical reviewer found the safety database to be adequate. Taiho submitted datasets in CDISC (STDM and ADaM) format which facilitated the FDA clinical reviewer to complete the review in a timely manner.

The clinical review primarily focused on data from Study 301 as this was the large controlled trial intended to support approval of TAS-102 for the indicated patient population. The placebo control allowed for the clinical reviewer to conduct an analysis of safety against the background of adverse events that commonly occur in patients with advanced cancer. The

safety population of Study 301 included 533 patients with advanced colorectal cancer who received TAS-102 and 265 who received placebo plus best supportive care. One patient in each arm dropped out prior to receiving TAS-102 or placebo. These patients were not included in the safety analysis; however, the applicant included these patients in their analyses of efficacy (i.e., ITT population). The clinical reviewer also reviewed safety data from other trials including Study J003-10040030; however, Study 301 was the primary focus of the safety review because it was the largest controlled trial in the intended population and the trial enrolled patients globally, including in the United States. Generally, the clinical reviewer found the safety profile of TAS-102 in these other studies consistent with the safety profile in Study 301.

In Study 301, median duration of treatment was 47 days in the TAS-102 arm versus 40 days for placebo (mean durations were 89 days and 48 days, respectively). *Comment: The short duration of therapy in both arms reflected the poor prognosis of patients with previously treated metastatic colorectal cancer. Nevertheless, this reviewer agrees that it is appropriate to take action on this application despite the lack of long-term safety data based on the improvement in overall survival and the short life expectancy of patients with previously treated colorectal cancer.* Despite the brief exposure of most patients, dose reductions were uncommon (13.7% in the TAS-102 arm) and only 3.6% of patients *primarily* discontinued TAS-102 due to an adverse event. The most common reason for treatment discontinuation across both arms was disease progression (refer to clinical review for details).

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

8.2.1 Deaths

The clinical reviewer found that the majority of deaths in Study 301 occurred due to progression of the underlying colorectal malignancy. The KM curves of OS in Section 7 of this review summarized the overall occurrence of deaths in Study 301. These curves provided some assurance of the relative safety of TAS-102.

A total of 68 patients died across both arms within 30 days of the last dose of TAS-102 or placebo. The proportion of patients dying within 30 days of the last dose was higher in the placebo arm (12.5% versus 6.5%) than in the TAS-102 arm. The most common reason listed for the death of these patients across both arms was disease progression (clinical or radiological). Taiho attributed one patient as dying due to a drug-related toxicity (Klebsiella pneumonia/septic shock) in the setting of febrile neutropenia.

In general, when looking at the incidence rate of specific fatal adverse events across arms, there were no consistent patterns in either the applicant's or the clinical reviewer's analyses to suggest that TAS-102 clearly caused the fatal events. Nevertheless, there was a potential difference in the rate of fatal infections with three cases in the TAS-102 (0.6%) arm and none in the placebo arm. These small numbers preclude any definitive statements regarding the risk of fatal infections; however, this reviewer acknowledges that TAS-102 can cause severe myelosuppression which can increase the risk for severe and life-threatening infections. Such risks related to cytotoxic chemotherapy are understood by trained oncologists and

communicated to patients via informed consent. Although there is some uncertainty regarding this risk (understanding that fatal infections can occur in patients with advanced cancer in the absence of cytotoxic chemotherapy), approval is warranted based on the overall survival effect observed in the entire population in Study 301.

8.2.2 SAEs

The Study 301 protocol defined (*non-verbatim definition*) a serious adverse event (SAE) as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; or was a congenital anomaly or birth defect. The protocol also stated that events that required intervention to prevent permanent impairment or damage or were an important medical event that could jeopardize the patient or require intervention to prevent one of the other serious outcomes listed above should also (usually) be considered serious.

The incidence of SAEs was higher in the placebo arm (33%) compared to the TAS-102 arm (29%). These incidence rates were similar to those assessed by the applicant (33.6% versus 29.6%; refer to clinical review for explanation of differences). The one category of serious adverse events that clearly was more common in TAS-102-treated patients was myelosuppression (5.3% versus 0). The clinical reviewer found that neutropenia as an SAE (reported at the MedDRA HLT level) occurred in 3.4% of TAS-102-treated patients versus 0 for placebo. The rate of febrile neutropenia (MedDRA preferred term) as an SAE was 2.6% for TAS-102 versus none for placebo. The rate of infections and infestations as SAEs was 4.5% among TAS-102-treated patients versus 4% among patients who received placebo.

8.2.3 Drop-outs and discontinuations due to adverse events

The number of patients who discontinued treatment (or placebo) due to an adverse event differed based on the specific dataset used. When assessing the adverse event dataset, 14% of patients in the placebo arm had an adverse event resulting in discontinuation compared to 10% in the TAS-102 arm. However, according to the disposition dataset, 4% of patients in the TAS-102 arm and 2% of patients in the placebo arm *primarily* discontinued due to an adverse event. Taiho stated that the discrepancy appeared related to the fact that many of the adverse events listed in the adverse event dataset occurred in the setting of disease progression [*comment: given that the rate of discontinuation (in the adverse event dataset) was higher in the placebo arm, this appears to be a reasonable explanation*]. Among patients randomized to receive TAS-102, the most frequent adverse events (irrespective of attribution) reported as leading to discontinuation were general physical health deterioration, fatigue, and dyspnea.

8.2.4 Common adverse events

Table 9, shows the clinical reviewer's analysis of adverse events (rounded to the nearest integer and occurring with a per-patient incidence rate of ≥ 10% in the TAS-102 arm). In general, the most common toxicities caused by TAS-102 were hematological and gastrointestinal in nature.

In general, the clinical reviewer's analysis was similar to that of the applicant's. In some cases, analyses of certain preferred terms differed by 1% or less. These differences were

related to minor differences in analysis methodology (e.g., in defining treatment-emergent adverse events) and the applicant's analyses did not appear to be systematically biased. Other differences in the incidence of adverse events in the table below compared to the label occurred because the label contains composite terms (e.g., asthenia/fatigue) or because the label used laboratory data to describe the rate of neutropenia, anemia, and thrombocytopenia (see below).

Table 9 Common AEs (preferred term), Study 301

	TAS-102 (N=533)		Placebo (N=265)	
	All Grades (%)	≥ Grade 3 (%)	All Grades (%)	≥ Grade 3 (%)
Nausea	48	2	24	1
Anemia	39	16	8	3
Decreased appetite	39	4	29	5
Fatigue	35	4	23	5
Diarrhea	32	3	13	0.4
Neutropenia	29	20	0	0
Neutrophil count decreased	28	16	0.4	0
Vomiting	28	2	14	0.4
White blood cell count decreased	27	10	0.4	0
Pyrexia	18	1	14	0.4
Asthenia	18	3	11	3
Platelet count decreased	15	2	2	0
Constipation	15	0.2	15	1
Abdominal pain	15	2	13	3
Cough	10	0.4	11	0.8
Dyspnea	10	2	13	3

In addition to the events described in the table, infections occurred more frequently among patients who received TAS-102 (27%) as compared to placebo (15%). Nasopharyngitis and urinary tract infections (both 4% versus 2%) were the most common infections which occurred more frequently in TAS-102-treated patients.

8.2.5 Laboratory tests

The most important laboratory-related toxicites were neutropenia, anemia, and thrombocytopenia. Table 10 shows laboratory abnormalities as described in the proposed product label. The percentiles are based on the number of patients with post-baseline samples rather than the safety evaluable population.

Table 10 Hematologic lab test abnormalities, Study 301

Lab Test	TAS-102			Placebo		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	67	27	11	1	0	0
Anemia	77	18	N/A	33	3	N/A
Thrombocytopenia	42	5	1	8	<1	<1

The clinical reviewer's results were similar to those of the applicant's. In general, the clinical reviewer found that the applicant's analyses tended to be more conservative and therefore acceptable for product labeling.

Based on these findings, the product label will contain a Warning informing medical professionals about the risk of severe or life-threatening myelosuppression.

8.3 Special safety concerns

8.3.1 Drug-demographic interactions

The clinical reviewer conducted analyses of adverse events by age range (≥ 65 years versus less than 65 years), gender, geographic area, and tumor location. In general, adverse events occurred at similar rates in the various groups. Meaningful conclusions of differences in adverse events were difficult to make because these were non-randomized subgroups, and in some cases, the number of patients in certain groups was small.

Despite limitations in the analyses, directed analyses appeared to show that patients 65 years of age or older experienced a higher incidence rate of hematological toxicity (e.g., the rate of Grade 3 or 4 neutropenia was 48% in patients 65 years of age or older versus 30% in younger patients). Information regarding the increased rate of myelotoxicity in older patients will be described in product labeling.

8.3.2 Additional in-depth analyses of specific events

Section 7.3.5 of the clinical review contained an analysis of Hy's law (laboratory criteria) to assess for hepatotoxicity. Based on laboratory data, a higher rate of patients in the placebo group met laboratory criteria for Hy's law (9% versus 6%). *Comment: Liver metastases are common in patients with metastatic colon cancer and as such, there is not a clear signal that TAS-102 increases the risk of hepatotoxicity.*

Section 6 of the label will describe a difference in pulmonary emboli across arms (2% for TAS-102 versus none on placebo). In regards to all venous thromboembolic events, the incidence was 3.6% versus 1.5%.

Finally, Taiho provided data in the NDA that identified interstitial lung disease (ILD) as an adverse reaction based on post-marketing reports from Japan. As of 24 Jul 2015, Taiho received 15 reports of interstitial pneumonia/interstitial lung disease of which 3 were fatal.

Taiho estimated that 7037 patients were exposed in Japan as of 24 Jul 2015 for an estimated incidence rate of 0.21%.

8.4 Discussion of primary reviewer's findings and conclusions

The clinical reviewer determined the safety database to be adequate for the intended indication given the overall survival effect observed in Study 301. The data in the label regarding safety were primarily based on the 533 patients who received TAS-102 and 265 patients who received placebo in Study 301.

The most common toxicities of TAS-102 were myelosuppression and gastrointestinal toxicites (and fatigue). Ultimately, the safety profile of TAS-102 is acceptable in a patient population with few treatment options based on the improvement in overall survival. The toxicities caused by TAS-102 are familiar to trained oncologists, and it is standard practice to monitor for these adverse reactions, institute treatment as necessary, and to dose modify therapy or discontinue therapy if necessary.

Comment: This reviewer agreed with the major conclusions in the clinical review. The incidence of adverse events in the clinical review was, in general, similar to (or the same as) those of the applicant. Small differences in the incidence rates of certain adverse events were not clinically significant.

9. Advisory Committee Meeting

The review team determined that an ODAC meeting was not necessary to review this application. The effects on OS were (statistically) robust based on the results observed in the pivotal clinical trial supported by the results of the Japanese trial, and trained oncologists are familiar with the types of toxicities caused by TAS-102 (an oral cytotoxic drug).

10. Pediatrics

Taiho submitted a Pediatric Research Equity Act (PREA) waiver request for all pediatric age groups. FDA's September 2005 Procedural Guidance, How to Comply with the Pediatric Research Equity Act, lists colorectal cancer as a condition that qualifies for a disease-specific waiver. The Division of Pediatric and Maternal Health (DPMH) agreed that pediatric studies under PREA are impracticable for the colorectal cancer indication and that a PREA waiver is appropriate for this application.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

The NDA contained a statement signed by the President and CEO of Taiho Oncology, Inc., that certified that Taiho did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.2 Financial disclosures

The majority of investigators reported that they did not enter into any financial arrangements whereby the value of compensation to the investigator would be expected to affect the outcome of the study as defined in 21 CFR 54.2(a). The applicant certified that the listed investigators referenced on Form 3454 did not disclose financial interests as defined in 21 CFR 54.2(b) or significant payments as described in 21 CFR 54.2(f).

A total of 100 investigators and 654 sub-investigators participated in Study 301. Taiho reported that financial disclosure information was reported by all 100 investigators and 644 sub-investigators. Disclosable financial interests were reported by four investigators or sub-investigators; however, only one participated in Study 301 (the others participated in Study J003-10040030). The single disclosable interest in Study 301 came from a sub-investigator at a Japanese site who reported receiving research funding, lecture's fees, and a "sideline" contract.

It is unlikely that this single financial interest compromised the results of Study 301. The primary investigator at the site enrolled 2.5% of the patient population and eliminating the results of this site would not change the study's conclusions.

11.3 GCP issues

Taiho (or designee) performed site audits of 13 sites and provided copies of audit certificates from these sites.

Taiho also included a statement in the Study 301 clinical study report that the study was conducted, and informed consent obtained according to the ethical principles that have their origins in the Declaration of Helsinki and in accordance with ICH Guidelines for Good Clinical Practice (GCP), and Title 21 CFR 312.50 through 312.70 as applicable and local and national laws and regulations relevant to the use of investigational therapeutic agents.

In general, the numbers of major protocol violations were similar between arms (see Section 3.2 of the clinical review). Although there were entry criteria violations reported in each arm, the types of violations were unlikely to have had a major impact on the overall study results.

11.4 OSI audits

DOP2 and OSI selected six clinical sites based on various factors including numbers of patients enrolled and site-specific efficacy results. All inspected sites were ex-U.S. including three sites in Japan, two in Spain, and one in Italy. All six sites received final inspection classifications of NAI (no action indicated).

11.5 Late-Cycle meeting

In order to expedite the action regarding this indication, this review was completed prior to the late-cycle meeting. No major issues are outstanding regarding this application except for agreement on final product labeling.

11.6 Other discipline consults

11.6.1 DRISK

DRISK concurred with DOP2 that a REMS is not necessary for TAS-102.

11.6.2 OPDP

OPDP provided advice regarding the Indications and Usage statement, Warnings and Precautions section, and Adverse Reactions section which resulted in changes to the label. Additional recommendations regarding Section 17 of the label are under consideration at this time.

11.6.3 Drug name review (DMEPA)

During the review of this application, DMEPA sent a letter on 3 Mar 2015 informing Taiho that the proposed trade name of Lonsurf was acceptable. The DMEPA review considered the name from a promotional perspective in consultation with DOP2 and OPDP. DMEPA also considered the name Lonsurf from a safety perspective (i.e., performed assessments for look-alike and sound-alike drugs) and found the name acceptable.

12. Labeling

FDA sent draft labeling recommendations to Taiho on 19 Aug 2015 prior to the date stipulated by the 21st Century Review Process. Labeling recommendations described below should not be considered final as labeling negotiations are ongoing.

In general, DOP2 revised all sections of the label for brevity and clarity. The remainder of this section of the review will only focus on high-level issues regarding the amended label submitted by Taiho. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections of the label (for example, if only minor edits were made to a section). This reviewer agreed with the recommendations made by the review teams that are described below.

> **6. Adverse Reactions:** FDA changed the cut-off value for most common adverse reactions from (b)(4)% to 10%. FDA updated the table to include adverse reactions occurring at a rate of ≥ 5%. FDA also included a paragraph indicating the overall difference in infections between arms.
>
> **7. Drug Interactions**: (b)(4)
>
> **8.5. Geriatric use:** FDA agreed with the inclusion of data regarding the higher incidence of hematologic toxicity in patients 65 years of age or older.
>
> **14. Clinical Studies:** FDA added certain eligibility criteria to put the study population in context.

Although (for brevity) the Division agrees with not including Kaplan-Meier curves for PFS in the label, the Division does not object to the use of the curves in promotional materials (as otherwise permitted in the United States under current law) and recognizes that the PFS effect was statistically significant (i.e., substantial evidence was submitted in the application to support a treatment effect on PFS). FDA agreed that Taiho could remove information regarding median PFS from the label (b) (4)

(b) (4)

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

This reviewer recommends regular approval of NDA 207981 based on substantial evidence of effectiveness from an adequate and well controlled trial (Study 301) supported by evidence from an additional randomized clinical trial conducted in Japan (Study J003-10040030) that was designed with a higher type 1 error rate. Study 301 established that TAS-102 can prolong the overall survival of patients with previously treated, metastatic colorectal cancer. This approval recommendation is contingent upon reaching agreement on labeling and PMRs.

13.2 Risk-benefit assessment

The recommendation for approval of this application is based on a statistically significant (but clinically modest) improvement on OS observed in Study 301. According to the May 2007 FDA Guidance Document regarding endpoints for cancer drugs (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf;), survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint. An effect on OS is considered regulatory evidence of clinical benefit used by the Agency to substantiate regular approval of a drug.

In general, because mCRC is an incurable disease [with the notable exception of patients who have oligometastatic disease (usually hepatic)], the goal of treatment for these patients is to prolong life and/or improve quality of life. The specific context for this application involves the treatment of patients who have received other therapies for metastatic colorectal cancer including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy [if appropriate (i.e., if the patient has RAS wild-type tumors]. Median survival (without treatment) in this setting is approximately five months as demonstrated in Study 301 and in the study supporting the approval of regorafenib (see below).

At this time, only regorafenib is approved for this patient population. FDA approved regorafenib on 27 Sep 2012 for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. FDA primarily based the approval decision on the basis of a single trial, BAY 73-4506/11650, which randomized 760 patients with previously treated mCRC to receive regorafenib plus best supportive care or placebo plus best supportive care. The trial demonstrated an improvement

in overall survival among regorafenib-treated patients compared to patients who received placebo [median OS for regorafenib was 6.4 months versus 5 months for placebo with HR of 0.77 (0.64, 0.94), p = 0.01]. Although the OS effect was modest, FDA approved regorafenib noting the absence of other effective treatment options and that physicians and patients would need to consider whether the modest improvement in OS was of sufficient magnitude to offset the toxicities caused by regorafenib including asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia, diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia.

Study 301 did not formally answer the question of how TAS-301 should be incorporated or sequenced into treatment plans for patients with mCRC in the context of the regorafenib approval. Nevertheless, Study 301 did enroll 18% of patients previously exposed to regorafenib and the HR in this group appeared consistent with the HR in patients who had not received prior regorafenib. Although FDA approved regorafenib shortly after the first patient was randomized in Study 301 (17 Jun 2012), regorafenib was not available in other areas of the world until later dates.

As stated earlier, TAS-102 extended the lives of patients with heavily pretreated mCRC, a patient population (generally) with a poor prognosis and few treatment options. In Study 301, patients who received TAS-102 in combination with best supportive care lived a median 1.8 months longer than patients who received placebo in combination with best supportive care [HR = 0.68 (0.58, 0.81), p < 0.001].

The effects on OS were supported by a statistically significant effect on progression free survival in Study 301 [HR 0.47 (0.40, .055), p < 0.001]. The estimated difference in median PFS was 0.3 months; however, the timing of scans in Study 301 likely influenced the estimates and the curves appeared to further separate after the medians. Nevertheless, the effects on PFS should be considered supportive of the OS results rather than as evidence of direct clinical benefit.

Finally, although not considered substantial evidence of effectiveness (e.g., due to difficulties with accurately determining a patient's PS with a clinician instrument as opposed to a PRO instrument), Taiho submitted supportive data regarding time to ECOG PS ≥ 2 favoring patients randomized to receive TAS-102 [estimated HR according to Taiho of 0.66 (95% CI: 0.56, 0.78)].

The primary risks related to TAS-102 are hematologic and gastrointestinal. Grade 3-4 neutropenia was the most common hematologic toxicity with 11% of patients experiencing Grade 4 neutropenia. Gastrointestinal toxicity was common (e.g., 48% of patients treated with TAS-102 experienced nausea compared to 24% on placebo); however, most of the gastrointestinal toxicity was Grade 1 or 2 in severity. Other non-gastrointestinal-related adverse reactions included asthenia/fatigue (52% versus 35%) and alopecia (7% versus 1%). Infections also occurred more frequently in TAS-102-treated patients (27% versus 15%).

There was a difference in pulmonary emboli in the two arms (2% TAS-102 versus 0 for placebo); however, there is some residual uncertainly related to the magnitude of this risk given the similar incidence of other VTEs between arms.

Overall, the toxicity profile of TAS-102 is acceptable when balancing the improvement in survival in a patient population with limited treatment options. Physicians and patients will need to individually assess the risk-benefit profile of TAS-102 to determine if treatment is appropriate for the patient. Importantly, the risk-benefit profile in Study 301 was determined in a patient population with ECOG PS 0 and 1. This reviewer cannot extrapolate the survival benefit (observed in Study 301) to patients with ECOG PS 2 or greater. Likewise, Study 301 did not enroll patients with brain metastasis or with ascities requiring drainage (within four weeks of enrollment). Consistent with other drugs intended for the treatment of patients with advanced cancer, risk will be managed through labeling. Risk is also managed by the fact that cytotoxic drugs for the treatment of patients with cancer are (generally) prescribed by clinical oncologists who are trained to monitor and manage toxicities related to these drugs.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

The review teams did not identify any REMS as necessary prior to a marketing authorization for TAS-102. TAS-102 will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious toxicities caused by anti-neoplastic drugs including cytotoxic chemotherapy. Standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

13.4 Recommendation for other postmarketing requirements and commitments

The following two PMRs were recommended by the Office of Clinical Pharmacology. These PMRs are described elsewhere in this review (e.g., Section 5.1) and involved completion of ongoing clinical trials.

- Complete the ongoing pharmacokinetic trial to determine an appropriate dose of Lonsurf 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.”

- Complete the ongoing pharmacokinetic trial to determine an appropriate dose of Lonsurf 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.”

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/s/

STEVEN J LEMERY
09/10/2015