

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207981Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207981

SUPPL # N/A

HFD # N/A

Trade Name Lonsurf

Generic Name trifluridine and tipiracil

Applicant Name Taiho Oncology, Inc.

Approval Date: September 22, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
New Molecular Entity Exclusivity – **5 years exclusivity**

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 018299

Trifluridine

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 018299

Trifluridine

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the

answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

N/A

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol TPU-TAS-102-301, 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 Chemotherapies"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol TPU-TAS-102-301, 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 Chemotherapies"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 57674	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND # N/A	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: **Studies were conducted** ! Explain:
in Japan and the product under
approval (tipiracil and
trifluridine) is approved in Japan

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Gina Davis
Title: RPM
Date: September 14, 2015

Name of Office/Division Director signing form: Office of Hematology and Oncology Products
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
09/25/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 8, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981 – Taiho Oncology, Inc. – Lonsurf (trifluridine/tipracil) –
Teleconference with Taiho – Labeling Discussions

Sponsor Attendees:

Eric C. Benn, President and CEO
Fabio Benedetti, Chief Medical Officer
Gihan Atalla, Pharmacovigilance Operations
Hirokazu Mizuguchi, Clinical Research
Lieselotte Bloss, Regulatory Affairs
Lisa Cooper, Regulatory Affairs
Mona Wahba, Medical Affairs
Paul Bebeau, Pharmacovigilance
Robert Winkler, Research and Development

FDA Attendees:

Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2)
Steven Lemery, M.D., Cross-Discipline Team Lead, DOP 2
Leigh Marcus, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2
Latonia Ford, BSN, MA, Regulatory Project Manager, Office of Surveillance and Epidemiology

Background:

On September 3, 2015, the Division of Oncology Products 2 requested a teleconference with Taiho Oncology, Inc. (Taiho) to discuss (b) (4) the Lonsurf package insert (PI).

Discussion:

DOP 2 asked whether (b) (4). Based on considerations regarding the definition/implications regarding the term (b) (4), Taiho agreed to remove the term because (b) (4) was already included in Section 6 of the label and conveyed the risk. FDA further requested additional information (b) (4) and would review for consideration regarding whether to include this in the label.

Action:

Taiho agreed to provide the rates of the (b) (4) via electronic (email) communication to DOP 2 and as a formal amendment to the NDA

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
09/22/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 207981 BLA #	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Lonsurf Established/Proper Name: trifluridine and tipiracil Dosage Form: Tablets, for oral use 15 mg and 20 mg		Applicant: Taiho Oncology, Inc. Agent for Applicant (if applicable): N/A
RPM: Gina Davis		Division: Division of Oncology Products 2
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: _____ <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 19, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H
 Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

BLAs: Subpart E
 Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart I
 Approval based on animal studies

Subpart H
 Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No N/A
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other - Bursts
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval Letter: 09/22/15
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> • Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included 09/14/15
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/19/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included 09/14/15
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/19/14
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 09/08/15
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s)) 	02/27/15 – Review 03/05/15 - Letter
❖ Labeling reviews (indicate dates of reviews)	RPM: 01/04/15– uploaded in DARRTs 09/16/2015 DMEPA: 06/17/15 and 09/10/15 DMPP: 09/03/2015 OPDP: 09/02/2015 Pediatric Review: 05/26/2015
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	02/15/15 – uploaded in DARRTs 08/13/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC July 8, 2015 – If PeRC review not necessary, explain: 	<p>full waiver granted due to indication</p>
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	<p>09/22/15 – Minutes – LC Meeting 09/22/15 – T-con mins 09/14/15 – Late Cycle mtg pkg 09/14/15 – Labeling proposal 08/26/15 – PMR/PMC 08/19/15 – Labeling-proposal 08/19/15 – I/R – carton/container 08/18/15 – I/R – PMR/PMC 07/23/15 – I/R 07/23/15 – I/R 07/23/15 – I/R 06/26/15 – I/R 06/26/15 – I/R 05/16/15 – I/R 05/16/15 – I/R 05/14/15 – I/R midcy com Agda 05/05/15 – I/R 05/05/15 – I/R for T-con (pst midcycle) 05/01/15 – I/R 04/14/15 – I/R 04/08/15 – I/R 02/23/15 – I/R 02/17/15 – Filing Ltr – 0 def. 02/17/15 – I/R FDA Snapshot 02/05/15 – I/R – CMC request 02/05/15 – FDA proposal to PI 02/04/15 – I/R 01/26/15 – I/R 01/16/15 – I/R 01/21/15 – I/R 01/09/15 – NDA – Ack Ltr 01/02/15 – I/R 12/31/15 – I/R 11/13/14 – Pre-submission Ack Ltr</p>
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	<p><u>Monthly Team Meetings</u> 07/28/15 – uploaded 09/16/15 05/26/15 – Memo - PMHS 06/12/15 – uploaded 09/16/15 04/22/15 - uploaded 09/16/15 03/25/15 – uploaded 09/16/15</p>
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<p>Pre-NDA Meeting – 07/31/2014 CMC Mtg – scheduled 12/5/14 (sponsor accepted CMC prelim comments on 11/27/14 – no mtg held)</p>
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<p>12/12/11</p>

<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	05/15/15 uploaded 09/21/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	09/18/15 – uploaded 09/22/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	N/A
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	09/22/15
Division Director Summary Review (<i>indicate date for each review</i>)	09/21/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	09/09/15
PMR/PMC Development Templates (<i>indicate total number</i>) PMRs (2)	09/22/15
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review - See CDTL Review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) 	08/21/15 – Filing Review 01/30/2015
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	03/27/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	08/24/15 – REMs Review – REMs not required
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	07/10/15 – OSI Summary of Clinical sites 07/10/15 06/04/15 06/01/15 05/29/15 05/29/15 05/20/15

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review 08/05/15 - concurrence found in statistical review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review 08/05/15
Statistical Review(s) (<i>indicate date for each review</i>)	08/05/15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review - concurrence in clin pharm review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review - concurrence in clin pharm review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 08/21/15- Filing 2/24/2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 09/18/15
• Supervisory Review(s) (<i>indicate date for each review</i>)	08/25/15
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	08/25/15 – Filing 2/3/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None August 19, 2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> August 19, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None

Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Granted by CMC – See page 2 of the CM review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable

Day of Approval Activities

<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input type="checkbox"/> Done



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: May 15, 2015 from 12:00 PM – 1:00 PM
Application Number: NDA 207981
Product Name: Lonsurf (trifluridine/tipiracil hydrochloride)
Indication: for the treatment of metastatic colorectal cancer
Applicant Name: Taiho Oncology, Inc.
Meeting Chair: Steven Lemery, M.D., MHS
Meeting Recorder: Gina M. Davis, M.T.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S., Medical Team Lead, OHOP/DOP 2
Leigh Marcus, M.D., Medical Officer, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, OHOP/DOP 2
Emily Fox, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Weishi Yuan, Ph.D., Statistical Reviewer, OB/DB V
Xianhua Cao, Ph.D. Clinical Pharmacology Reviewer, OCP/DCP V
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, OCP/DCP V
Olen Stephens, Ph.D., Branch Chief, OPQ/ONDP

Eastern Research Group

Patrick Zhou

APPLICANT ATTENDEES

Christopher Zergebel, Project Management
Cliff Ding, Statistics
Eric C. Benn, President and CEO
Fabio Benedetti, Chief Medical Officer
Gihan Atalla, Pharmacovigilance Operations
Hirokazu Mizuguchi, Clinical Research
Hiroshi Ambe, Clinical Development (calling from Japan)
Julie Boisvert, Regulatory Affairs
Kazuhiko Baba, CMC (calling from Japan)
Kenichiro Yoshida, Clinical Pharmacology
Lieselotte Bloss, Regulatory Affairs
Lisa Cooper, Regulatory Affairs
Lukas Makris, Statistics
Mona Wahba, Medical Affairs
Owen Vaughan, Regulatory Affairs (calling from London, UK)

Paul Bebeau, Pharmacovigilance

(b) (4) (consultant)

Rachel Mathew, Regulatory Affairs CMC (calling from Japan)

Racquel Weaver, Clinical Operations

Robert Winkler, Research and Development

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical
- CMC

Discussion during the meeting: Taiho Acknowledged FDA's response and no discussion occurred.

3.0 INFORMATION REQUESTS

Clinical Pharmacology

Clinical Pharmacology information request to be sent regarding systemic exposure data in patients with renal impairment.

Discussion during the meeting: FDA stated that an information/request regarding systemic exposure data in patients with renal impairment will be requested as FDA that the population PK analysis suggests an increase of 30 – 80% in moderate renal impairment. Taiho stated that that data was submitted to the IND. FDA acknowledged submission of the data but wants Taiho to perform the initial analysis. Taiho acknowledged FDA's response and will perform the initial analysis.

CMC

CMC IR sent at the end of April. Taiho provided a response via electronic (email) communication on May 14, 2015.

Discussion during the teleconference: FDA acknowledged receipt for Taiho's email submission but is unable to comment at this time because the information has not been reviewed.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Currently there are no plans for a REMs

Discussion during the teleconference: Taiho Acknowledged FDA's response and no discussion occurred.

5.0 ADVISORY COMMITTEE MEETING

Currently there are no plans to hold an Advisory Committee Meeting.

Discussion during the teleconference: Taiho Acknowledged FDA's response and no discussion occurred.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting is September 18, 2015.

Discussion during the teleconference: Taiho asked that if FDA could re-schedule the late cycle meeting if we move our date for approval. FDA stated that there is flexibility on the calendar with respect to scheduling meetings and a meeting could be re-scheduled if necessary. Taiho acknowledged FDA's response.

7.0 POSTMARKETING REQUIREMENTS (PMRs) AND POSTMARKETING COMMITMENTS (PMCs)

Two potential clinical pharmacology PMRs

- CSR TO-TAS-102-106: Hepatic impairment study
- CSR TO-TAS-102-107: Renal impairment study

Discussion during the meeting: FDA stated that the potential for two PMRs regarding the hepatic study, Study CSR TO-TAS-102-106 and the renal impairment study, Study CSR TO-TAS-102-107. FDA further stated that Taiho Oncology should provide language and milestone timelines with respect to the PMRs. Taiho stated that patients were enrolled and being in enrolled in the mild and moderate cohorts under both studies and estimate that the final CSR will be available for both studies in July 2017.

ADDITIONAL COMMENT

Taiho asked if FDA still planned to communicate proposed labeling and postmarketing commitment requests by August 31, 2015, as noted in the filing letter. FDA stated that proposed labeling and postmarketing commitment requests will be addressed on or before August 31, 2015.

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/s/

GINA M DAVIS
09/21/2015

**March Monthly Meeting
March 25, 2015**

NDA 207981

Product: Lonsurf (trifluridine/tipiracil hydrochloride), 15 mg and 20 mg tablets
 Submission Date: December 19, 2014
 Received Date: December 19, 2014
 Sponsor: Taiho Oncology, Inc.
 Proposed: 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.

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process.

Agenda Items:

1. Review Status:

- Priority Review requested
- Exclusivity Request: Waiver request for Pediatric studies
- The clinical development of Lonsurf has been conducted under IND 57674

2. Dates Milestone Letters Must Issue

Milestone	Standard review – (12 month review)	Priority review – (8 month review)
<i>Acknowledgment Letter</i>	<i>Under review</i>	<i>Under review</i>
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a “Notification of Review Status” letter.	Target Date: Tuesday, February 17, 2015	Target Date: Tuesday, February 17, 2015

Deficiencies Identified Letter (74 Day Letter)	Target Date: Tuesday, March 3, 2015	Target Date: Tuesday, March 3, 2015
FINAL Action Letter Due	Target Date: Friday, December 19, 2015	Target Date: Wednesday, August 19, 2015

3. Upcoming/TBD Internal Team Meetings:

- Filing Meeting: February 2, 2015
- Mid-Cycle Meeting: May 12, 2015
- Late-Cycle Meeting: TBA
- Labeling Meetings: TBA
- Team Meetings
 - March 25, 2015
 - April 22, 2015
 - May 15, 2015
 - June 12, 2015
 - July 17, 2015
 - August – TBA
 - September – TBA
 - October – TBA
 - November - TBA

4. Discussion Points

DRISK – safety signals

- The two semi-significant items DRISK noted with this application is increased myelosuppression and GI issues. DRISK understands with fluoropyrimidine-based treatment it is common as is with TAS-102. In the RECURSE trial, close to 70% individuals experienced. It was managed effectively with reduction in dose, delay in cycle initiation and G-CSF such that only 3 pts d/ced treatment due to hematologic AEs. The other issue was increased GI disorders (nausea (48.4%), diarrhea (31.9%), vomiting (27.8%), constipation (15.2%) , abdominal pain (14.8%) were the most common of GI disorders observed in greater 10% of pts receiving TAS-102 although the incidence of Grade ¾ AEs was low.

DRISK would like to discuss these issues with the clinical team.

Currently DRISK has not identified any signals that would be included in the boxed warning.

Inspections

- Taiho was contacted by the Official Establishment Inventory (OEI) office to update the FEI number listed on the EDRLS website for their Saitama facility. Saitama facility is the TPI (drug substance) manufacturing plant.

The FDA Inspection Division advised Taiho that a FEI number had previously been assigned to their Saitama facility (3002646390). This number differs from the one listed on the web site (30108773059) which has been referenced in the NDA submissions.

Taiho stated that the OEI coordinator confirmed that they should use the older FEI number (3002646390).

Additionally, Taiho noticed that the address that OEI office used in their e-mail correspondence wasn't correct (the postal code is wrong). The address that appears on the EDRLS website is the correct address. Taiho plans to make this change via SPL submission, and update Form FDA 356h. Taiho intends to notify the Parsippany District Office of the changes.

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/s/

GINA M DAVIS
09/16/2015

**April Monthly Meeting
April 22, 2015**

NDA 207981

Product: Lonsurf (trifluridine/tipiracil hydrochloride), 15 mg and 20 mg tablets
Submission Date: December 19, 2014
Received Date: December 19, 2014
Sponsor: Taiho Oncology, Inc.
Proposed: 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.

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process.

Agenda Items:

1. Review Status:

- Priority Review requested
- Exclusivity Request: Waiver request for Pediatric studies
- The clinical development of Lonsurf has been conducted under IND 57674

2. Dates Milestone Letters Must Issue

- FINAL Action Letter Due

Friday, December 19, 2015 – We may take action early.

3. Upcoming/TBD Internal Team Meetings:

- Filing Meeting: February 2, 2015
- Mid-Cycle Meeting: May 13, 2015
- Late-Cycle Meeting: TBA
- Labeling Meetings:
 - Labeling Meeting # 1 – June 17, 2015 - Clinical and Stats
 - Labeling Meeting # 2 - June 23, 2015 - Clinical and Clinical Pharmacology
 - Labeling Meeting # 3 - July 7, 2015 - Clinical and Clinical Pharmacology
 - Labeling Meeting # 4 – July 13, 2015 - Clinical, CMC and DMEPA
 - Labeling Meeting # 5 - July 23, 2015 - Clinical
 - Labeling Meeting # 6 - July 30, 2015 – Clinical
 - Labeling Meeting # 7 – August 18, 2015 – Clinical, PMHS, and Nonclinical

Disciplines	Sections of Label	Number of Meetings
Clinical Team and Statistics Team	Indications and Usage (1) Clinical Studies (14)	One labeling meeting
Clinical Team Clinical Pharmacology Team	D&A (2), Drug Inter. (7) Geriatric Use (8.5), Hep I. (8.6) Renal I (8.7), PD (12.2) PK (12.3)	Two labeling meetings (1.5 hours - each mtg)
CMC Team DMEPA Clinical Team	Dosage Forms Strength (3) Description (11) How Supplied (16)	One labeling meeting (1.5 hours)
Clinical Team	Contraindications (4) W. and P. (5) Adverse Reactions (6) Patient Counseling (17)	Two labeling meetings
Clinical Team Maternal Health Team Nonclinical Team	Bone Marrow Supp. (5.1) Pregnancy (8.1) Female/Males Repro. (8.3) Pediatric Use (8.4) Mech. of Action (12.1) Nonclinical (13)	One labeling meeting (1.5 hours)

- Team Meetings
 - March 25, 2015
 - April 22, 2015
 - May 15, 2015
 - June 12, 2015
 - July 17, 2015
 - August 20, 2015
 - September 16, 2015
 - October – 2, 2015(?)

- Wrap-up Meeting – September 21, 2015 (?)

I am experiencing a few issues with Panorama and should have everything addressed by close of business today. The 21st Century Review Calendar will be updated to coincide with Panorama and will be sent to the team today.

The Post Midcycle Communication Teleconference and Late Cycle Meeting are currently tentatively scheduled, but I want to ensure that I my dates align with Panorama. These dates will be available to the team by the end of the day.

4. **Discussion Points**

5. **Additional Issues – Requests for Information**

The following information was requested from Taiho;

- Methods validation studies for Lonsurf
 - Method, current version
 - Samples and Reference Standards
 - Equipment
 - MSDS and Certificates of Analysis

Response not provided to date.

- An updated version of the label, tracked changes, in PLR format.

Response not provided to date.

- Define further the variable RECADY (see “comments” in ADLB dataset) with examples. Specifically, how did you review the median amount of days patients with Grade 4 neutropenia, anemia, thrombocytopenia, took to recover to Grade 1 (p2088 of CSR).

Taiho provided a response on April 17, 2015.

- CMC IRs will be conveyed to sponsor first week of May.

Inspections

- Taiho was contacted by the Official Establishment Inventory (OEI) office to update the FEI number listed on the EDRLS website for their Saitama facility. Saitama facility is the TPI (drug substance) manufacturing plant.
- The FDA Inspection Division advised Taiho that a FEI number had previously been assigned to their Saitama facility (3002646390). This number differs from the one listed on the web site (30108773059) which has been referenced in the NDA submissions.
- Taiho stated that the OEI coordinator confirmed that they should use the older FEI number (3002646390).

- Additionally, Taiho noticed that the address that OEI office used in their e-mail correspondence wasn't correct (the postal code is wrong). The address that appears on the EDRLS website is the correct address. Taiho plans to make this change via SPL submission, and update Form FDA 356h. Taiho intends to notify the Parsippany District Office of the changes.

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/s/

GINA M DAVIS
09/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 14, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA proposed labeling

Dear Dr. Cooper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

We also refer to the Lonsurf (trifluridine/tipiracil) package insert (PI) submitted with your application and to your counter-proposal received via electronic (email) communication on August 26, 2015 and formally submitted to your NDA on August 31, 2015. Attached to this memorandum is our counter- proposal to your August 31, 2015 submission which includes feedback from the Office of Prescription Drug Promotion and the Division of Medical Policy Programs regarding the patient package insert.

Please provide a response by close of business September 18, 2015 or sooner. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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

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/s/

GINA M DAVIS
09/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 26, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981; Taiho Oncology, Inc. – Lonsurf (trifluridine and tipiracil)
Proposed PMC/PMRs language

Dear Dr. Cooper,

Please refer to your December 19, 2014, New Drug Application (NDA) on December 19, 2015, for your product Lonsurf (trifluridine and tipiracil). We are currently reviewing your submission and propose the following Post Market Requirements (PMRs) in draft format. Taiho Oncology Inc. (Taiho) will be required to provide reasonable timelines for completion of these PMRs including dates for submission of the final study protocol, trial completion date and submission of the final study report. Taiho is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

PMRs

Clinical Pharmacology

1. 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.

PMR Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/2017
	Final Report Submission:	12/2017

2. 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.”

PMR Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/2017
	Final Report Submission:	12/2017

Please review the PMRs listed above and provide a response by close of business September 2, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drugs Evaluation and Research

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/s/

GINA M DAVIS
08/26/2015

**June Monthly Meeting
June 12, 2015**

NDA 207981

Product: Lonsurf (trifluridine/tipiracil hydrochloride), 15 mg and 20 mg tablets
Submission Date: December 19, 2014
Received Date: December 19, 2014
Sponsor: Taiho Oncology, Inc.
Proposed: 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.

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process.

Agenda Items:

1. Review Status:

- Priority Review requested
- Exclusivity Request: Waiver request for Pediatric studies
- The clinical development of Lonsurf has been conducted under IND 57674

2. Dates Milestone Letters Must Issue

- FINAL Action Letter Due
Friday, December 19, 2015 – We may take action early.

3. Upcoming/TBD Internal Team Meetings:

- Filing Meeting: February 2, 2015
- Mid-Cycle Meeting: May 13, 2015
- Late-Cycle Meeting: TBA
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 - Labeling Meeting # 3 - July 7, 2015 - Clinical and Clinical Pharmacology
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CMC Team DMEPA Clinical Team	Dosage Forms Strength (3) Description (11) How Supplied (16)	One labeling meeting (1.5 hours)
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Clinical Team Maternal Health Team Nonclinical Team	Bone Marrow Supp. (5.1) Pregnancy (8.1) Female/Males Repro. (8.3) Pediatric Use (8.4) Mech. of Action (12.1) Nonclinical (13)	One labeling meeting (1.5 hours)

- Team Meetings
 - March 25, 2015
 - April 22, 2015
 - May 15, 2015
 - June 12, 2015
 - July 17, 2015
 - August 20, 2015
 - September 16, 2015
 - October – 2, 2015(?)

- Wrap-up Meeting – September 21, 2015 (?)

I am experiencing a few issues with Panorama and should have everything addressed by close of business today. The 21st Century Review Calendar will be updated to coincide with Panorama and will be sent to the team today.

The Post Midcycle Communication Teleconference and Late Cycle Meeting are currently tentatively scheduled, but I want to ensure that I my dates align with Panorama. These dates will be available to the team by the end of the day.

4. **Discussion Points**

5. **Additional Issues – Requests for Information**

The following information was requested from Taiho;

May 1, 2015

I/R – clinical request

Request for clinical information - RECOUSE Grade 3, Grade 4 and Grade 5 AE issues

- *Taiho provided a response on May 12, 2015 and June 9, 2015.*

May 4, 2015

I/R CMC

Request for CMC information - Propose acceptance criteria for water content and hardness at both release and stability.

- *Taiho provided a response on June 3, 2015.*

May 5, 2015

General Advice – Post Midcycle Meeting Teleconference

Division respectfully requested a post-mid cycle meeting with Taiho Oncology on May 15, 2015

- *Taiho provided a response via email communication on May 7, 2015.*

May 5, 2015

Labeling PMR/PMC Discussions

Information request regarding proposed edits/changes to the carton and container for Lonsurf.

- *Taiho provided a response on May 20, 2015*

May 14, 2015

Post Midcycle Agenda

Agenda for the Post Midcycle meeting provided to Taiho.

May 16, 2015

I/Rs - Statistics and Clinical Pharmacology

Request for statistical information - Original protocols and all amendments in track changes

- *Taiho provided a response on June 5, 2015.*

Request from clinical pharmacology - Population PK data and raw data sets.

- *Taiho provided a response on June 5, 2015.*

6. Inspections

OSI

Barcelona, Spain

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Kashiwa-city, Japan 181-8611

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Kita-Adachi-Gun, Saitama 3620806

Japan

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Chiba-city, Chiba 2608717

Japan

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Madrid, Spain

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Facilities

All sites have been inspected, awaiting feedback on the following inspections;

- Taiho Pharmaceutical Co Ltd FEI 3002646390 (API)
scheduled for inspection May 10 – May 15, 2015
- Taiho Pharmaceutical Corporation FEI 3010872322 (Finished Dosage
Form) – scheduled for inspection May 18 – May 22, 2015
- [REDACTED] (b) (4) (testing) –
scheduled for inspection [REDACTED] (b) (4)

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/s/

GINA M DAVIS
09/16/2015

**July Monthly Meeting
July 28, 2015**

NDA 207981

Product: Lonsurf (trifluridine/tipiracil hydrochloride), 15 mg and 20 mg tablets
Submission Date: December 19, 2014
Received Date: December 19, 2014
Sponsor: Taiho Oncology, Inc.
Proposed: 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.

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process.

Agenda Items:

1. Review Status:

- Priority Review requested
- Exclusivity Request: Waiver request for Pediatric studies
- The clinical development of Lonsurf has been conducted under IND 57674

2. Dates Milestone Letters Must Issue

- FINAL Action Letter Due
Friday, December 19, 2015 – We may take action early.

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Labeling Meeting # 6 - July 30, 2015 – Clinical
Labeling Meeting # 7 – August 18, 2015 – Clinical, PMHS, and Nonclinical

Disciplines	Sections of Label	Number of Meetings
Clinical Team and Statistics Team	Indications and Usage (1) Clinical Studies (14)	One labeling meeting
Clinical Team Clinical Pharmacology Team	D&A (2), Drug Inter. (7) Geriatric Use (8.5), Hep I. (8.6) Renal I (8.7), PD (12.2) PK (12.3)	Two labeling meetings (1.5 hours—each mtg)
CMC Team DMEPA Clinical Team	Dosage Forms Strength (3) Description (11) How Supplied (16)	One labeling meeting (1.5 hours)
Clinical Team	Contraindications (4) W. and P. (5) Adverse Reactions (6) Patient Counseling (17)	Two labeling meetings
Clinical Team Maternal Health Team Nonclinical Team	Bone Marrow Supp. (5.1) Pregnancy (8.1) Female/Males Repro. (8.3) Pediatric Use (8.4) Mech. of Action (12.1) Nonclinical (13)	One labeling meeting (1.5 hours)

- Team Meetings
 - March 25, 2015
 - April 22, 2015
 - May 15, 2015
 - June 12, 2015
 - July 28, 2015
 - August 20, 2015
 - September 16, 2015
 - October – 2, 2015(?)

- Wrap-up Meeting – September 21, 2015 (?)

The Late Cycle Meeting
Internal Meeting - August 20, 2015
Sponsor Meeting – September 18, 2015
Meeting Package to Sponsor – September 9, 2015

4. **Discussion Points**

- Proposed timelines with respect to the Lonsurf marketing application.
- Taiho response to DMF I/R
- July 30, 2015 labeling meeting - will this meeting be canceled?

5. **Additional Issues – Requests for Information**

The following information was requested from Taiho since the last monthly meeting;

- July 13, 2015 – Received Taiho’s response to FDA’s June 26, 2015, request Clinical Pharmacology I/R – labeling issues regarding concomitant use of Lonsurf.
- July 24, 2015 - Received Taiho’s response to FDA’s July 7, 2015, request CMC I/R - [REDACTED] ^{(b) (4)} regarding performance qualification studies.

6. **Inspections**

OSI

Barcelona, Spain

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Kashiwa-city, Japan 181-8611

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Kita-Adachi-Gun, Saitama 3620806

Japan

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Chiba-city, Chiba 2608717

Japan

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Madrid, Spain

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Pisa, Italy

Results from inspections - Adhered to the applicable statutory requirements and FDA regulations – NAI

Facilities

CMC

All sites have been inspected

- Taiho Pharmaceutical Co Ltd FEI 3002646390 (API) scheduled for inspection May 10 – May 15, 2015
- Taiho Pharmaceutical Corporation FEI 3010872322 (Finished Dosage Form) – scheduled for inspection May 18 – May 22, 2015
- [REDACTED] (b) (4) (testing) – scheduled for inspection [REDACTED] (b) (4)

Method Validation

The following methods were verified and found acceptable for quality control and regulatory purposes:

- Assay for Tipiracil
- Related Substances for Tipiracil
- Assay for FTD/TPI, 15 and 20mg
- Related Substances for FTD/TPI, 15 and 20mg

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/s/

GINA M DAVIS
09/16/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 19, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981; Taiho Oncology, Inc. – Lonsurf (trifluridine and tipiracil)
DMEPA – Advice and Information

Dear Dr. Cooper,

Please refer to your December 19, 2014, New Drug Application (NDA) on December 19, 2015, for your product Lonsurf (trifluridine and tipiracil).

Currently your application is under review and we have the following comments and requests for information.

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

1. Container Labels
 - a. 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 (64842-102^{(b) (4)}) and Lonsurf 20 mg/8.19 bottles (64842-102^{(b) (4)}) 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^[1].
 - b. Revise the statement on the side panels of container labels, ^{(b) (4)} to read, “Usual Dose: See prescribing information”.
 - c. 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).

2. Carton Labeling
 - a. See comments 1(a) and 1(b).

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

Please provide a response to the aforementioned request by close of business September 2, 2015.
If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drugs Evaluation and Research

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GINA M DAVIS
08/19/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 19, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA proposed labeling

Dear Dr. Cooper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

We also refer to the Lonsurf (trifluridine/tipiracil) package insert (PI) submitted with your application. Attached to this memorandum is our proposal to your PI. Please review and provide feedback. Please note, the Office of Prescription Drug Promotion and the Division of Medical Policy Programs are currently reviewing the PI and may have additional edits and comments.

Please provide a response by close of business September 2, 2015. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA proposed labeling

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

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GINA M DAVIS
08/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 18, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981; Taiho Oncology, Inc. – Lonsurf (trifluridine and tipiracil)
Proposed PMC/PMRs language

Dear Dr. Cooper,

Please refer to your December 19, 2014, New Drug Application (NDA) on December 19, 2015, for your product Lonsurf (trifluridine and tipiracil). We are currently reviewing your submission and propose the following Post Market Requirements (PMRs) in draft format. Taiho Oncology Inc. (Taiho) will be required to provide reasonable timelines for completion of these PMRs including dates for submission of the final study protocol, trial completion date and submission of the final study report. Taiho is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

PMRs

Clinical Pharmacology

1. 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.

PMR Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/2017
	Final Report Submission:	12/2017

2. 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.”

PMR Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	09/2017
	Final Report Submission:	12/2017

Please review the PMRs listed above and provide a response by close of business September 2, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drugs Evaluation and Research

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/s/

GINA M DAVIS
08/19/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 23, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information - CMC

Dear Ms. Cooper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comments and requests for information.

1. Provide samples of the container closure system including the bottle and closures for both the (b) (4) (commercial) and (b) (4) (primary stability) bottles.
2. Identify the location of the (b) (4) data for the (b) (4) bottles.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
07/23/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 23, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981 – Taiho Oncology – Lonsurf - Late Cycle
Teleconference/Meeting

Dear Ms. Cooper,

The Division of Oncology Products 2 has scheduled a late cycle teleconference/meeting with Taiho Oncology, Inc. to discuss the status of the review.

Late Cycle Teleconference/Meeting

Friday, September 18, 2015
11:00 AM – 12:00 PM
Please provide call-in information

You will receive the Late Cycle Meeting Package on or before September 9, 2015. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/23/2015

**PeRC Meeting Minutes
July 8, 2015**

PeRC Members Attending:

Lynne Yao

Wiley Chambers

George Greeley

Freda Crooner

Tom Smith

Daiva Shetty

NON-RESPONSIVE

Lily Mulugeta

Robert "Skip" Nelson

Kevin Krudys

Belinda Hayes

NON-RESPONSIVE

Shrikant Pagay

Rosemary Addy

Greg Reaman

NON-RESPONSIVE

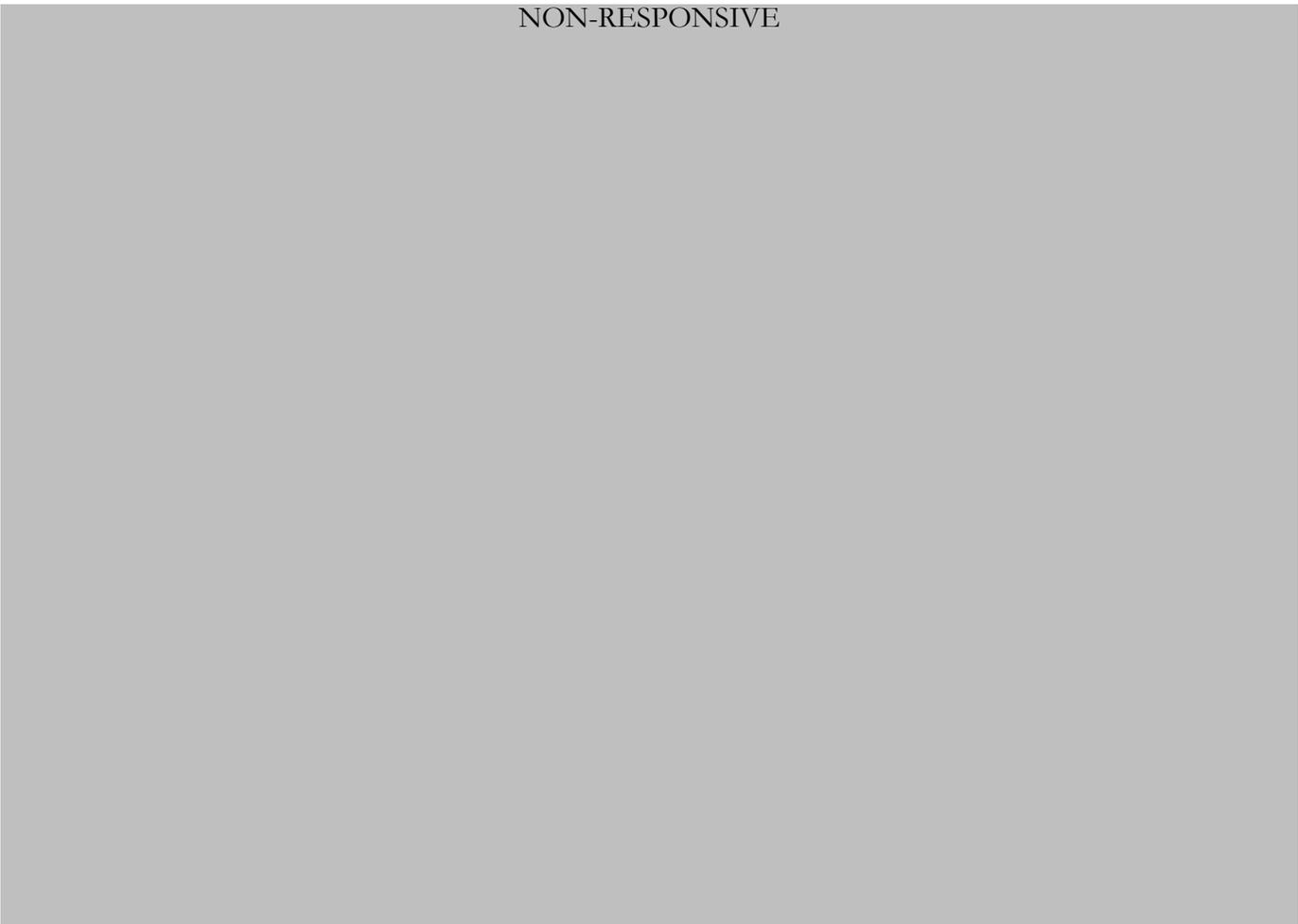
Adrienne Hornatko-Munoz

Barbara Buch

Olivia Ziolkowski

Agenda

NON-RESPONSIVE



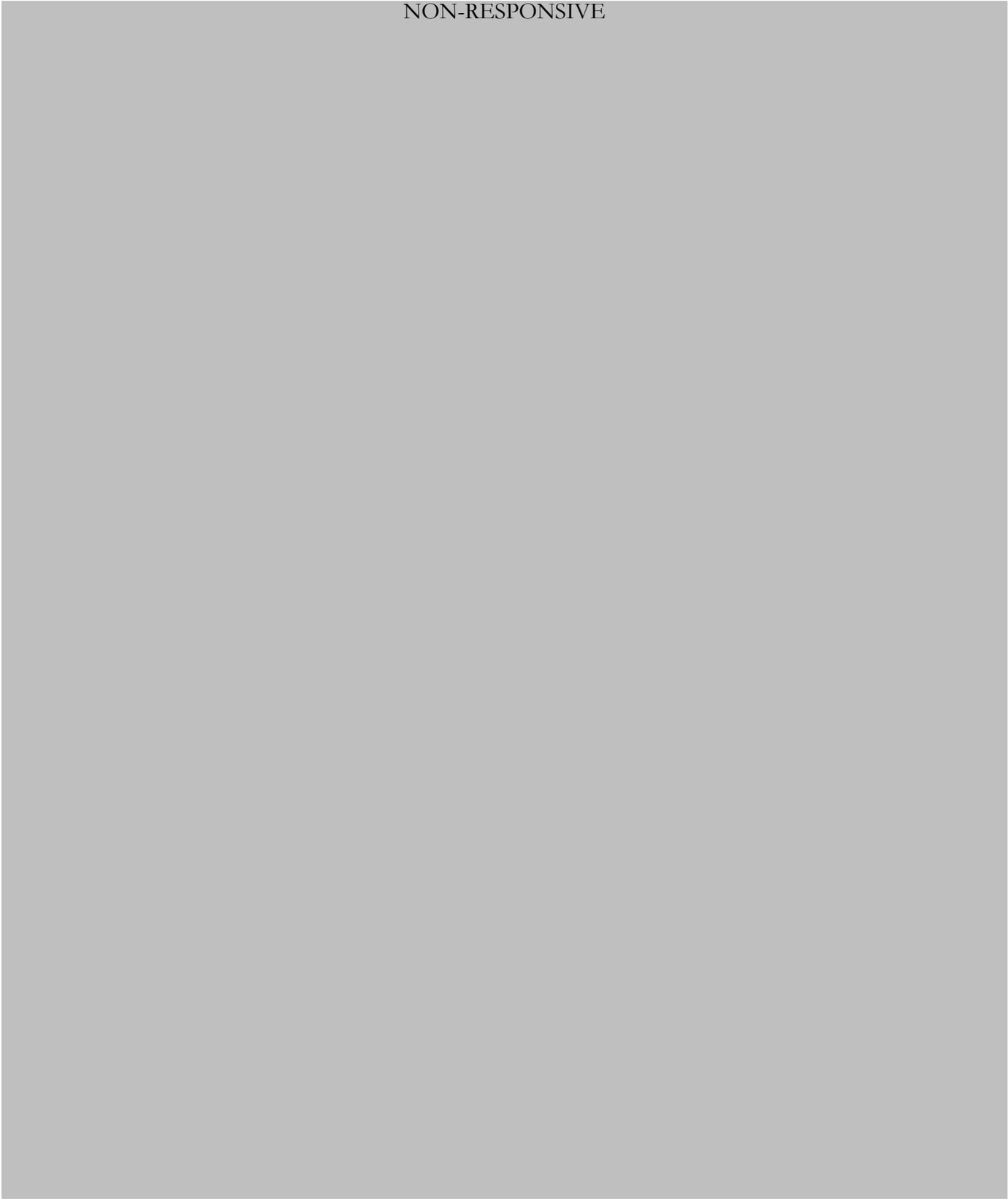
	<i>NDA</i>	<i>207981</i>	<i>Lonsurf (trifluridine and tipiracil) Full Waiver</i>	<i>For the treatment of metastatic colorectal cancer</i>	
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NON-RESPONSIVE



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NON-RESPONSIVE



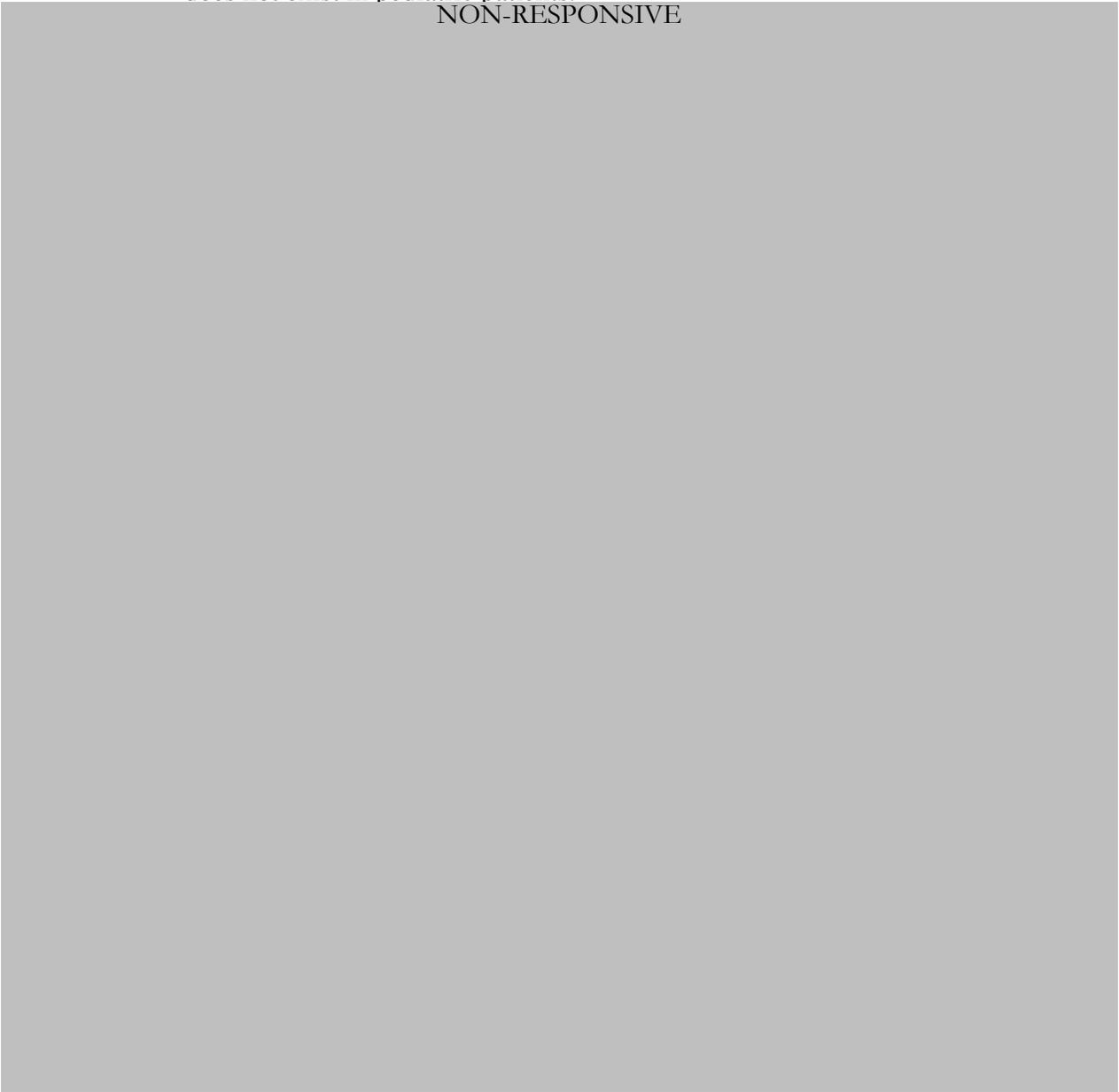
Lonsurf (trifluridine and tipiracil) Full Waiver

- Proposed Indication: For the treatment of metastatic colorectal cancer

- ***PeRC Recommendations:***

- The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impractical because the disease/condition does not exist in pediatric patients.

NON-RESPONSIVE



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/s/

GETTIE AUDAIN
07/22/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 26, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information – Clinical Pharmacology

Dear Ms. Cooper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comments and requests for information.

Proposed labeling - Section 7 (Drug Interactions) of the Lonsurf Package Insert (PI).

1. Submit data and/or scientific justification to support the proposed labeling statement

(b) (4)
(D) (4)

2. (b) (4)

3. (b) (4)

Please provide a response to the aforementioned requests by close of business July 9, 2015. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
06/26/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 16, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information - statistics

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comment and request for information.

Please submit the original protocol and all amendments, with track changes for each version.

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/16/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 16, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information - statistics

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comments and requests for information.

1. Reference is made to the study report titled “Population pharmacokinetic analysis for FTD and TPI following TAS-102 administration in selected clinical studies in patients with solid tumor cancers” (Study No. 12DA25). In page 65 and 103, there appears to be an association between BSA vs unexplained inter-individual variability (η) of clearance based on the final models for FTD and TPI, suggesting BSA may also be an influential covariate for clearance. It should be noted that inclusion of a covariate in population PK model may be based upon physiological plausibility regardless of the statistical significance. Update your population PK report by adding BSA as a covariate at clearance to support BSA adjusted dosing and re-evaluate the effect of other covariates (e.g., creatinine clearance and albumin) on clearance.
2. Submit the raw datasets and analysis of renal function effects on PK from study TPU-TAS-102-301. The distributions of the observed steady state concentration and derived AUCs for each renal function subgroups shall also be submitted.

Please provide a response to the aforementioned requests by close of business June 9, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/16/2015

APPEARS THIS WAY ON ORIGINAL

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

NDA#: 207981

PRODUCT PROPRIETARY NAME: Lonsurf

ESTABLISHED/GENERIC NAME: TAS-102

APPLICANT/SPONSOR: Taiho Oncology, Inc.

PREVIOUSLY APPROVED INDICATION/S:

- (1) _____
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) _____
- (2) _____
- (3) _____
- (4) _____

BLA/NDA STAMP DATE: December 19, 2014

PDUFA GOAL DATE: December 19, 2015

SUPPLEMENT TYPE: N/A

SUPPLEMENT NUMBER: N/A

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?

Did the sponsor submit an Agreed iPSP? Yes No

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes No

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes No

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. Provide justification for Waiver:

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

basal cell and squamous cell skin cancer

bladder

breast

cervical

colorectal

endometrial

esophageal

cancer (continued):

follicular lymphoma

gastric

hairy cell leukemia

hepatocellular

indolent non-Hodgkin lymphoma

lung (small & non-small cell)

multiple myeloma

oropharynx (squamous cell)

ovarian (non-germ cell)

pancreatic

prostate

refractory advanced melanoma

renal cell

uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. **Age groups included in the deferral request:**
2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**
3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)**
 - a. Adult studies are completed and ready for approval
 - b. Additional safety or effectiveness data needed (**describe**)
 - c. Other (**specify**)
4. **Provide projected date for the submission of the pediatric assessment (deferral date):**
5. **Did applicant provide certification of grounds for deferring assessments?** Yes No
6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. **Has a pediatric plan been submitted to the Agency?** Yes No
2. **Does the division agree with the sponsor's plan?** Yes No
3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** Yes No

- a. **Protocol Submission:**
- b. **Study Completion:**
- c. **Study Submission:**

4. **Has a Written Request been issued?** Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. **Has a PPSR been submitted?** Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Types of Studies/Study Design:

Nonclinical Studies:

Clinical Studies:

Age group and population (indication) in which study will be performed:

This section should list the age group and population exactly as it is in the plan.

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.

Number of patients to be studied or power of study to be achieved:

Example:

Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.

Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs
Patients must have a negative pregnancy test if female..*

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety will be the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.

Timing of assessments:

Example :baseline, week 1, 4, and 6

Statistical information (statistical analyses of the data to be performed):

Example:

Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

Division comments on sponsor proposal to satisfy PREA:

PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? **Yes** **No** If yes, did sponsor follow plan?

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week, 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

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/s/

GINA M DAVIS
05/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 14, 2015
From: Gina Davis, Senior Regulatory Health Project Manager, CDER/OHOP/DOP2
Subject: Agenda for Midcycle Communication - Lonsurf (trifluridine and tipiracil)

Meeting Date/Time: Friday, May 15, 2015 from 12:00 PM – 1:00 PM

Application Number: NDA 207981
Product Name: Lonsurf (trifluridine and tipiracil)
Indication: Treatment of metastatic colorectal cancer
Applicant Name: Taiho Oncology, Inc.
Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Gina Davis

FDA TENTATIVE ATTENDEES

Steven Lemery, M.D., M.H.S., Medical Team Lead, OHOP/DOP 2
Leigh Marcus, M.D., Medical Officer, OHOP/DOP 2
Sandra Casak, M.D., Medical Officer, OHOP/DOP 2
Gina Davis, M.T. Senior Regulatory Health Project Manager, OHOP/DOP 2
Emily Fox, Ph.D., Nonclinical Reviewer, OHOP/DHOT
Whitney Helms, Ph.D., Nonclinical Supervisor, OHOP/DHOT
Weishi Yuan, Ph.D., Statistical Reviewer, OB/DB V
Kun He, Ph.D., Statistical Team Lead, OB/DB V
Xianhua Cao, Ph.D. Clinical Pharmacology Reviewer, OCP/DCP V
Jingyu (Jerry) Yu, Ph.D., Pharmacometrics Reviewer, OCP/ DMP
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, OCP/DCP V
Olen Stephens, Ph.D., Branch Chief, OPQ/ONDP

SPONSOR ATTENDEES

Christopher Zergebel, Project Management
Cliff Ding, Statistics
Eric C. Benn , President and CEO
Fabio Benedetti, Chief Medical Officer
Gihan Atalla, Pharmacovigilance Operations
Hirokazu Mizuguchi, Clinical Research
Hiroshi Ambe, Clinical Development (calling from Japan)
Julie Boisvert, Regulatory Affairs
Kazuhiko Baba, CMC (calling from Japan)
Kenichiro Yoshida, Clinical Pharmacology

Lieselotte Bloss, Regulatory Affairs
Lisa Cooper, Regulatory Affairs
Lukas Makris, Statistics
Mona Wahba, Medical Affairs
Owen Vaughan, Regulatory Affairs (calling from London, UK)
Paul Bebeau, Pharmacovigilance
(b) (4) (consultant)
Rachel Mathew, Regulatory Affairs CMC (calling from Japan)
Racquel Weaver, Clinical Operations
Robert Winkler, Research and Development

Introductions

FDA and Taiho Oncology, Inc.

Introductory Comments

Steve Lemery, Cross-Discipline Team Leader

Significant Review Issues

Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical
- CMC

Information Requests (IR)

CMC IR sent at the end of April; awaiting response from Taiho.

Clinical Pharmacology information request to be sent regarding systemic exposure data in patients with renal impairment

Risk Management Update

Currently there are no plans for a REMs

Advisory Committee Meeting Plans

Currently there are no plans to hold an Advisory Committee Meeting.

Proposed Date for Late-Cycle Meeting

The proposed date for the late cycle meeting is September 18, 2015.

Postmarketing Commitments (PMCs)/Postmarketing Requirements (PMRs)

Two potential clinical pharmacology PMRs

- CSR TO-TAS-102-106: Hepatic impairment study
- CSR TO-TAS-102-107: Renal impairment study

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/s/

GINA M DAVIS
05/15/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 14, 2015
From: Gina Davis, Senior Regulatory Health Project Manager, CDER/OHOP/DOP2
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Product Name: Lonsurf (trifluridine and tipiracil)
Indication: Treatment of metastatic colorectal cancer
Applicant Name: Taiho Oncology, Inc.
Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Gina Davis

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Leigh Marcus, M.D., Medical Officer, OHOP/DOP 2
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Lisa Cooper, Regulatory Affairs
Lukas Makris, Statistics
Mona Wahba, Medical Affairs
Owen Vaughan, Regulatory Affairs (calling from London, UK)
Paul Bebeau, Pharmacovigilance
[REDACTED] (b) (4) (consultant)
Rachel Mathew, Regulatory Affairs CMC (calling from Japan)
Racquel Weaver, Clinical Operations
Robert Winkler, Research and Development

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FDA and Taiho Oncology, Inc.

Introductory Comments

Steve Lemery, Cross-Discipline Team Leader

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Currently there are no significant issues regarding the following disciplines;

- Clinical
- Statistics
- Clinical Pharmacology
- Nonclinical
- CMC

Information Requests (IR)

CMC IR sent at the end of April; awaiting response from Taiho.

Facilities

All sites acceptable except three pending inspection

- Taiho Pharmaceutical Co Ltd FEI 3002646390 (API) – scheduled for inspection May 10 – May 15, 2015
- Taiho Pharmaceutical Corporation FEI 3010872322 (Finished Dosage Form) – scheduled for inspection May 18 – May 22, 2015
- [REDACTED] (b) (4) (testing) – scheduled for inspection [REDACTED] (b) (4)

Clinical Pharmacology information request to be sent regarding systemic exposure data in patients with renal impairment

Risk Management Update

Currently there are no plans for a REMs

Advisory Committee Meeting Plans

Currently there are no plans to hold an Advisory Committee Meeting.

Proposed Date for Late-Cycle Meeting

The proposed date for the late cycle meeting is September 18, 2015.

Postmarketing Commitments (PMCs)/Postmarketing Requirements (PMRs)

Two potential clinical pharmacology PMRs

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- CSR TO-TAS-102-107: Renal impairment study

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/s/

GINA M DAVIS
05/14/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 5, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981; Taiho Oncology; Request for teleconference – Post Mid-Cycle Meeting

Dear Ms. Boisvert,

Please refer to your December 19, 2014, New Drug Application (NDA) submitted under section 505(b) of the Food, Drug and Cosmetic Act (FDCA) for your product Lonsurf for the treatment of colorectal cancer.

The Division of Oncology Products 2 (DOP 2) respectfully requested a teleconference with Taiho Oncology to discuss the highlights of the May 13, 2015, mid-cycle meeting. Per your May 4, 2015, electronic (email) communication, you have agreed to meet with DOP 2, via teleconference scheduled for May 15, 2015, from 12:00 PM – 1:00 PM.

The following information will be discussed with you and your team.

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for the late-cycle meeting
- Updates regarding plans for the AC meeting (if an AC meeting is anticipated)
- Other projected milestones dates for the remainder of the review cycle

Please provide call-in information regarding this teleconference by May 13, 2015. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
05/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 5, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – Labeling Negotiations - Carton and Container

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Please also refer to your carton label and container label submitted on December 19, 2014. Currently your submission is under review and we have proposed edits and changes to the carton and container.

Please review the enclosures and provide a response by May 15, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES
Carton Labeling
Container Labeling

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

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/s/

GINA M DAVIS
05/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 1, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comment and request for information.

1. For RECOURSE, what is the definition of “treatment-related AE” and what did you use to flag this in ADAE dataset?
2. When using the Treatment Emergent Analysis Flag (TRTEMFL), there were 524 (98.3) subjects on the TAS-102 arm and 247 (93.2) subjects on placebo that were flagged, however these values are listed on p103 of the CSR under “any adverse events”. We would like to double check that all AEs listed in the ADAE dataset were “treatment-emergent.”
3. Did you count only subjects with an AE within 30 days of the last dose of drug in your analyses and tables (CSR p103)? When using the Follow-up Flag (FUPFL), incidence of “any AE” with or without using FUPFL were identical at 524 (98.3) subjects on the TAS-102 arm and 247 (93.2) subjects on placebo. Did you use the subjects with FUPFL flag (53 events in 29 patients) for any AEs or any SAEs calculation? We note that for subjects that had the last dose of their study medicine less than 30 days before the SAE (therefore not analyzing any FUPFL data), the incidence was 156 (29%) in TAS-102 and 88 (33%).
4. For Grade ≥ 3 AE using FUPFL there were 366 (68.7) subjects on TAS-102 and 134 (50.6) subjects on placebo, and without censoring for FUPFL, there were 369 (69.2) and 134 (50.6) respectively, according to our analysis integrating all grades 3, 4, and 5. Since our numbers are off by as many as 4 subjects (depending on use of FUPFL), please review our attached list of subjects with Grade 3, 4, and 5 AE in AT deleting FUPFL population, and account for whom we did not include that is included in your analysis, and an explanation of why you have included them.

5. In your draft label, you list that “In the RECOURSE study, 9.4% of patients in the Lonsurf group received G-CSF.” I see that p416 of CSR lists 50 subjects. We identified 51 subjects in the ADCM dataset with the flag named CMGCSFFL. Who did you exclude from the analysis of GCSF use and why were they excluded?

Please provide a response as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES

RECOUSE Grade 3, Grade 4 and Grade 5 AE FUFLAG Document
GCSF Chart

RECOURSE: Grade 3 and 4 AE	
Subj ID	Treatment Arm
101-002	Placebo
101-003	TAS-102
101-004	Placebo
102-001	TAS-102
102-002	TAS-102
102-004	Placebo
102-005	TAS-102
103-003	TAS-102
103-012	TAS-102
103-015	TAS-102
104-001	TAS-102
104-002	TAS-102
150-002	Placebo
150-003	TAS-102
150-004	TAS-102
150-005	TAS-102
150-009	TAS-102
150-011	TAS-102
150-013	TAS-102
150-015	TAS-102
151-001	TAS-102
151-003	Placebo
153-001	TAS-102
153-002	Placebo
154-003	TAS-102
154-004	TAS-102
154-005	TAS-102
154-008	TAS-102
154-009	Placebo
155-004	TAS-102
200-001	TAS-102
200-003	TAS-102
200-004	TAS-102
200-006	TAS-102
201-001	TAS-102
201-007	TAS-102
201-008	TAS-102
201-009	Placebo
201-014	Placebo
202-002	TAS-102
202-003	TAS-102
202-004	TAS-102
202-008	TAS-102
202-010	Placebo

202-011	Placebo
204-003	TAS-102
204-007	Placebo
204-008	TAS-102
205-001	TAS-102
205-002	TAS-102
205-004	Placebo
205-007	Placebo
205-009	Placebo
205-010	TAS-102
205-011	TAS-102
205-013	TAS-102
205-015	Placebo
205-016	Placebo
205-018	Placebo
205-019	Placebo
206-001	TAS-102
206-002	TAS-102
206-003	Placebo
206-004	TAS-102
206-005	TAS-102
206-006	Placebo
206-007	TAS-102
206-013	TAS-102
206-016	TAS-102
206-017	TAS-102
251-005	TAS-102
251-010	TAS-102
302-001	Placebo
302-002	TAS-102
302-003	TAS-102
304-002	TAS-102
304-003	TAS-102
304-005	TAS-102
306-001	TAS-102
306-002	Placebo
306-003	TAS-102
306-004	Placebo
307-002	TAS-102
309-002	Placebo
309-003	TAS-102
310-004	TAS-102
312-003	TAS-102
351-004	Placebo
351-005	TAS-102
351-006	TAS-102

351-007	TAS-102
351-009	TAS-102
351-015	TAS-102
352-002	TAS-102
352-004	TAS-102
354-003	Placebo
354-004	TAS-102
354-006	TAS-102
355-002	TAS-102
355-004	TAS-102
355-005	TAS-102
355-007	TAS-102
355-008	TAS-102
355-010	TAS-102
355-013	TAS-102
355-014	TAS-102
355-016	TAS-102
355-017	Placebo
355-018	TAS-102
355-021	Placebo
355-022	TAS-102
355-026	TAS-102
356-001	TAS-102
356-004	TAS-102
356-005	TAS-102
356-006	TAS-102
356-007	Placebo
356-008	TAS-102
356-010	TAS-102
356-012	TAS-102
356-017	TAS-102
356-020	TAS-102
356-021	TAS-102
356-022	TAS-102
356-023	Placebo
356-024	TAS-102
356-025	TAS-102
357-001	TAS-102
357-003	TAS-102
358-001	TAS-102
358-003	Placebo
358-005	TAS-102
358-007	TAS-102
358-008	TAS-102
358-010	TAS-102
360-001	TAS-102

360-004	TAS-102
360-006	TAS-102
360-007	TAS-102
360-009	TAS-102
360-011	TAS-102
361-001	TAS-102
361-002	TAS-102
361-003	Placebo
361-006	TAS-102
361-008	TAS-102
361-009	TAS-102
361-012	Placebo
361-013	TAS-102
362-001	Placebo
362-005	TAS-102
362-008	Placebo
362-011	Placebo
363-001	TAS-102
363-002	TAS-102
363-004	Placebo
400-004	TAS-102
400-005	TAS-102
400-006	TAS-102
401-001	TAS-102
401-002	Placebo
401-003	TAS-102
401-005	TAS-102
401-008	TAS-102
402-001	TAS-102
402-004	TAS-102
402-005	TAS-102
402-006	TAS-102
403-001	TAS-102
403-002	TAS-102
403-005	TAS-102
403-007	TAS-102
403-011	TAS-102
403-014	Placebo
403-016	TAS-102
405-002	TAS-102
405-006	TAS-102
405-011	TAS-102
405-012	TAS-102
405-014	TAS-102
405-015	Placebo
405-016	TAS-102

405-018	Placebo
406-002	TAS-102
406-003	Placebo
406-006	TAS-102
406-007	Placebo
406-009	TAS-102
406-010	TAS-102
450-003	Placebo
453-002	TAS-102
453-003	TAS-102
455-002	Placebo
456-002	TAS-102
500-001	TAS-102
500-002	TAS-102
501-001	TAS-102
502-001	TAS-102
502-002	TAS-102
502-004	Placebo
550-002	TAS-102
551-004	Placebo
552-001	TAS-102
552-003	TAS-102
552-004	TAS-102
554-001	TAS-102
554-003	Placebo
554-006	TAS-102
559-001	TAS-102
559-002	Placebo
559-003	TAS-102
559-004	TAS-102
559-005	TAS-102
559-007	Placebo
559-009	Placebo
559-010	Placebo
560-001	Placebo
560-003	TAS-102
562-007	TAS-102
562-008	TAS-102
562-009	Placebo
562-011	TAS-102
562-012	TAS-102
562-014	TAS-102
562-017	TAS-102
562-019	TAS-102
562-024	Placebo
562-025	TAS-102

562-026	Placebo
562-028	TAS-102
562-029	TAS-102
562-032	TAS-102
563-002	TAS-102
564-005	TAS-102
564-006	TAS-102
564-007	TAS-102
564-008	Placebo
564-013	Placebo
566-001	TAS-102
567-001	TAS-102
567-003	TAS-102
569-002	Placebo
569-004	TAS-102
570-002	TAS-102
572-001	TAS-102
572-004	TAS-102
572-005	TAS-102
572-007	TAS-102
573-002	TAS-102
575-001	Placebo
575-003	TAS-102
575-004	TAS-102
576-002	TAS-102
576-004	TAS-102
576-005	TAS-102
577-001	Placebo
577-005	TAS-102
577-006	Placebo
578-001	TAS-102
578-002	TAS-102
578-005	TAS-102
578-006	TAS-102
600-002	TAS-102
600-004	TAS-102
600-006	TAS-102
602-003	TAS-102
602-004	Placebo
602-008	TAS-102
602-009	Placebo
602-010	TAS-102
603-001	Placebo
603-004	TAS-102
603-005	TAS-102
603-008	TAS-102

604-002	TAS-102
604-003	TAS-102
604-004	TAS-102
604-005	TAS-102
604-006	TAS-102
604-007	TAS-102
604-008	TAS-102
604-009	Placebo
604-010	TAS-102
604-011	Placebo
604-012	TAS-102
604-013	Placebo
604-014	TAS-102
604-016	Placebo
604-018	Placebo
604-021	Placebo
604-023	TAS-102
604-024	TAS-102
604-025	TAS-102
604-026	TAS-102
604-028	TAS-102
604-030	Placebo
604-032	TAS-102
604-033	Placebo
604-035	TAS-102
604-038	TAS-102
605-001	TAS-102
606-003	TAS-102
606-005	TAS-102
606-006	TAS-102
606-007	TAS-102
606-008	TAS-102
606-010	Placebo
606-011	TAS-102
606-015	TAS-102
607-003	Placebo
607-008	TAS-102
607-009	TAS-102
608-001	Placebo
608-002	TAS-102
608-004	TAS-102
608-008	Placebo
608-009	TAS-102
608-015	Placebo
610-004	TAS-102
610-005	Placebo

610-021	Placebo
610-022	TAS-102
610-023	TAS-102
651-002	Placebo
652-001	TAS-102
652-002	TAS-102
652-003	TAS-102
652-004	TAS-102
700-003	TAS-102
700-004	TAS-102
700-005	TAS-102
700-007	TAS-102
700-008	TAS-102
700-009	Placebo
700-010	TAS-102
700-012	TAS-102
700-013	TAS-102
700-015	TAS-102
700-018	TAS-102
700-020	TAS-102
700-022	TAS-102
701-001	TAS-102
701-002	TAS-102
701-004	TAS-102
701-007	TAS-102
701-008	TAS-102
701-010	TAS-102
701-011	Placebo
701-013	TAS-102
701-014	Placebo
702-001	TAS-102
702-003	Placebo
702-004	Placebo
702-005	TAS-102
702-006	Placebo
703-001	Placebo
703-002	TAS-102
703-003	TAS-102
703-004	TAS-102
703-005	TAS-102
703-007	TAS-102
704-002	TAS-102
704-003	TAS-102
704-007	Placebo
704-009	TAS-102
704-011	TAS-102

704-012	TAS-102
704-013	TAS-102
705-002	Placebo
705-003	Placebo
705-004	Placebo
705-005	TAS-102
705-006	Placebo
705-007	TAS-102
705-012	TAS-102
705-013	TAS-102
705-014	TAS-102
705-015	Placebo
705-016	TAS-102
705-017	TAS-102
705-018	TAS-102
705-020	TAS-102
705-022	TAS-102
705-028	TAS-102
705-033	TAS-102
706-003	TAS-102
706-004	Placebo
706-005	TAS-102
706-008	TAS-102
706-010	Placebo
706-011	TAS-102
706-012	TAS-102
706-013	TAS-102
706-014	TAS-102
706-015	Placebo
707-001	TAS-102
707-003	TAS-102
707-004	Placebo
707-006	TAS-102
707-010	Placebo
707-012	TAS-102
707-013	TAS-102
707-017	Placebo
707-021	TAS-102
707-023	TAS-102
708-001	TAS-102
708-004	Placebo
708-005	TAS-102
708-006	TAS-102
708-007	TAS-102
708-009	Placebo
708-011	TAS-102

709-004	TAS-102
709-006	TAS-102
709-009	TAS-102
709-011	TAS-102
709-014	Placebo
709-015	TAS-102
709-016	Placebo
709-017	Placebo
709-019	Placebo
709-020	Placebo
709-021	TAS-102
710-002	TAS-102
710-006	TAS-102
710-008	TAS-102
710-009	TAS-102
710-011	TAS-102
711-003	Placebo
711-007	TAS-102
711-010	Placebo
711-011	Placebo
711-012	TAS-102
711-013	TAS-102
711-020	Placebo
711-022	Placebo
712-001	TAS-102
712-002	Placebo
712-005	TAS-102
712-006	TAS-102
712-008	TAS-102
712-010	Placebo
712-011	TAS-102
712-012	Placebo
712-013	TAS-102
712-016	TAS-102
713-001	TAS-102
713-003	TAS-102
714-001	TAS-102
714-003	TAS-102
714-005	TAS-102
714-008	TAS-102
715-001	TAS-102
715-002	Placebo
715-003	TAS-102
715-004	TAS-102
715-005	TAS-102
715-006	TAS-102

715-007	TAS-102
715-010	TAS-102
716-001	Placebo
716-002	Placebo
716-003	Placebo
716-005	TAS-102
716-007	TAS-102
716-008	TAS-102
716-010	TAS-102
716-011	Placebo
716-012	Placebo
717-003	TAS-102
717-005	TAS-102
717-007	TAS-102
717-010	TAS-102
717-011	TAS-102
718-001	TAS-102
718-002	TAS-102
718-004	TAS-102
718-005	TAS-102
718-006	Placebo
718-010	TAS-102
719-001	TAS-102
719-003	Placebo
719-004	TAS-102
719-006	TAS-102
719-008	TAS-102
719-010	TAS-102
719-012	TAS-102

RECOURSE: Grade 5 AE	
Subj ID	Treatment Arm
101-002	Placebo
102-001	TAS-102
103-005	Placebo
104-001	TAS-102
150-007	Placebo
200-006	TAS-102
204-009	TAS-102
205-019	Placebo
302-001	Placebo
304-003	TAS-102
304-005	TAS-102

354-002	Placebo
355-013	TAS-102
357-004	Placebo
358-001	TAS-102
361-003	Placebo
362-006	Placebo
401-002	Placebo
403-002	TAS-102
403-010	Placebo
405-015	Placebo
406-007	Placebo
455-002	Placebo
500-005	TAS-102
554-003	Placebo
559-007	Placebo
560-001	Placebo
562-024	Placebo
567-003	TAS-102
575-003	TAS-102
602-003	TAS-102
604-002	TAS-102
606-004	Placebo
606-009	Placebo
703-001	Placebo
704-008	Placebo
705-028	TAS-102
706-004	Placebo
706-015	Placebo
709-018	TAS-102
711-003	Placebo
711-011	Placebo
712-012	Placebo
712-015	Placebo
716-001	Placebo
716-012	Placebo
718-002	TAS-102

GCSF Chart

104-002
200-006
205-001
205-011
356-022
358-005
360-001
360-009
400-004
400-006
401-001
401-003
401-005
401-008
402-004
403-005
403-011
403-016
453-002
500-002
502-001
550-002
552-004
554-006
563-002
564-006
566-001
572-001
573-001
573-002
600-004
604-004
604-005
604-024
604-032
607-009
700-003
701-002
703-004
703-007
705-018
705-022
706-003
706-005
706-008
713-001
713-003
714-003
716-005
716-007
717-010

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/s/

GINA M DAVIS
05/01/2015



NDA 207981

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Taiho
Attention: Julie Boisvert
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Julie Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lonsurf (trifluridine/tipiracil hydrochloride (FTD/TPI) film-coated tablets 15 and 20 mg).

We will be performing methods validation studies on Lonsurf (trifluridine/tipiracil hydrochloride (FTD/TPI) film-coated tablets 15 and 20 mg), as described in NDA 207981.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Analytical procedures (trifluridine/tipiracil hydrochloride (FTD/TPI) film-coated tablets
Assay for FTD/TPI (15 and 20 mg)
Related substances for FTD/TPI (15 and 20 mg)

Samples and Reference Standards

2 x 300 mg of tipiracil hydrochloride reference standard
2 x 200 mg of trifluridine reference standard
2 x 300 mg of tipiracil hydrochloride drug substance

(b) (4)

100 tablets Lonsurf (trifluridine/tipiracil hydrochloride (FTD/TPI) film-coated tablets 15 mg
100 tablets Lonsurf (trifluridine/tipiracil hydrochloride (FTD/TPI) film-coated tablets 20 mg

Equipment

1 column 4.6 mm x 150 mm

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
04/14/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 8, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf (trifluridine/tipiracil) – FDA request for information

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf (trifluridine/tipiracil).”

Currently your application is under review and we have the following comment and request for information.

Define further the variable RECADY (see “comments” in ADLB dataset) with examples. Specifically, how did you review the median amount of days patients with Grade 4 neutropenia, anemia, thrombocytopenia, took to recover to Grade 1 (p2088 of CSR).

Please provide a response to the aforementioned request by April 16, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
04/08/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207981

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Taiho Oncology, Inc.
202 Carnegie Center, Suite 100
Princeton, NJ 08540

ATTENTION: Julie Boisvert
Senior Manager, Regulatory Affairs

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) dated and received December 19, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trifluridine/Tipiracil Hydrochloride Tablets, 15 mg and 20 mg.

We also refer to your correspondence, dated and received December 22, 2014, requesting review of your proposed proprietary name, Lonsurf. We have completed our review of the proposed proprietary name, Lonsurf and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your December 22, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Gina Davis, Regulatory Project Manager in the Office of New Drugs at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
03/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 23, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf [*Proposed*] (trifluridine/tipiracil) –
FDA request for information

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Currently your submission is under review and we have the following comments and requests for information.

1. Submit the raw datasets for your exposure-response analysis for efficacy and safety.
2. You are also welcome to submit any preliminary results of exposure-response for efficacy and safety.

Please provide a response to the aforementioned requests by close of business March 9, 2015. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/23/2015



NDA 207981

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) dated December 19, 2014, received December 19, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Lonsurf (trifluridine and tipiracil), 15 mg and 20 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is December 19, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 31, 2015. In addition, the planned date for our internal mid-cycle review meeting is May 13, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we identified labeling issues which we conveyed to you in our February 5, 2015, communication. In this communication we requested that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 16, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
02/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 17, 2015
From: Gina M. Davis RPM, DOP2/OHOP/CDER/FDA
Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: NDA 207981 – Lonsurf (trifluridine and tipiracil)

We are requesting your assistance in populating the attached tables for your New Molecular Entity, Lonsurf, that is currently under review in the Division, this information will be posted publically, if approved, at the FDA drug snapshot website:

<http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>

We are asking this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly-approved drugs and biologics.

The website will include information on the study design, the results of efficacy and safety studies, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. It is not intended to replace or replicate the package insert, which are intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focus on subgroup data and analyses
- Links to PI for the product and to the FDA reviews at Drugs@FDA
- Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the NDA submission.

We are requesting you submit this information no later than March 2, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparat r/control (n=) n (%)	Treatmen t arm (n=) n (%)	Differenc e (95% CI)	Comparat or/control (n=) n (%)	Treatmen t arm (n=) n (%)	Differenc e (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication ²			
All other than controlled trials conducted for this indication ³			
Controlled trials conducted for other indications ⁴			

¹ *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

**Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)**

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

**Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population
(Events ≥ 2% of drug-treated subjects and more frequent than placebo)¹**

MedDRA System Organ Class Preferred Term	Male (N=)		Female (N=)	
	Comparat or/Contro l (n=) n (%)	Total Drug X (n=) n (%)	Comparat or/Contro l (n=) n (%)	Total Drug X (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

MedDRA Preferred Term	Age ≥17-<65 years (N=)		Age ≥65 years (N=)	
	Comparat or/Control (n=) n (%)	Total Drug X (n=) n (%)	Comparat or/Control (n=) n (%)	Total Drug X (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

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/s/

GINA M DAVIS
02/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 5, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf [*Proposed*] (trifluridine/tipiracil) –
FDA comments/proposals to the Lonsurf label

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Currently your application is under review and we have performed a preliminary review of your label. Please review the label below containing our edits and address our comments accordingly.

Please provide a response to the aforementioned request by February 16, 2015. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

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/s/

GINA M DAVIS
02/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 4, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf [*Proposed*] (trifluridine/tipiracil) –
FDA request for information

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Currently your application is under review and we have the following comments and requests for information.

We encourage you to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **Trifluridine + Tipiracil** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005) via the links below.

<http://inside.fda.gov:9003/downloads/cder/officeofsurveillanceandepidemiology/ucm349744.pdf>

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073107.pdf>.

If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.

Please provide a response to the aforementioned requests by close of business February 9, 2015. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
02/05/2015



NDA 207981

INFORMATION REQUEST

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA 207981) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lonsurf (trifluridine/tipiracil hydrochloride) Film-coated tablet, FTD/TPI (15/7.065 mg) and (20/9.420 mg).

We also refer to your December 19, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

- 1. Provide batch analysis for the drug substance batches used in the manufacture of supporting drug product batches.*
- 2. In the risk evaluation, you mention that Drug Substance (solubility in a range of pH values), amount of [REDACTED] (b) (4) and packaging are low risk factors with regard to dissolution. The amount of [REDACTED] (b) (4) and the amount of [REDACTED] (b) (4), on the other hand, are medium risk factors. Provide data to support the risk evaluation conclusions.*
- 3. The developmental parameters of the dissolution method have not been adequately justified. Provide experimental data to support the selection of the dissolution medium, pH, and agitation/rotation speed. In addition, comment on whether or not sink conditions are maintained for the duration of dissolution testing.*
- 4. The discriminating ability of the proposed dissolution method is not demonstrated. Please submit experimental data to support the discriminating power of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the*

selected dissolution method should compare the dissolution profiles of the target product and variant formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., \pm 10-20% change to the specification-ranges of these variables).

If you have any questions, please contact me, Rabiya Laiq, Regulatory Business Process Manager at (240) 402-6153. Please respond by February 10, 2015.

Sincerely,

{See appended electronic signature page}

Olen Stephens, Ph.D.
Branch Chief, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

OLEN M STEPHENS
02/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 21, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf [*Proposed*] (trifluridine/tipiracil) –
FDA response to Taiho request for clarification

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Please also refer to your January 20, 2015, electronic (email) communication requesting to submit the EU RMP in February 2015. We have reviewed your request and have the following comment and request for information.

We concur that a Risk Evaluation and Mitigation Strategy (REMS) is not required at this time, and a final determination will be made during the review process of this NDA. Your proposal to submit the proposed EU RMP at the time you submit to EU authorities near the end of February is acceptable. Please submit the EU RMP as an amendment to the NDA in section 1.16 Risk Management Plans.

Please ensure that your January 20, 2015, request for clarification is formally submitted to your NDA. If you have any additional questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
01/21/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 26, 2015
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 207981– Taiho Oncology – Lonsurf [*Proposed*] (trifluridine/tipiracil) –
FDA request for information

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Currently your application is under review and we have the following comment and request for information.

Please review the comment below and provide a response.

A total of ___(X)___ investigators and ___(Y)___ sub-investigators participated in Study TPU-TAS-102-301. Of these, financial disclosure information was obtained from ___(X)___ investigators and ___(Y)___ sub-investigators, one of whom reported a conflict of interest.

- Please limit this request to those who participated in the study.
- Please also complete this statement for investigators in Study J003-10040030.

Please provide a response to the aforementioned request by close of business February 2, 2015. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
01/26/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 16, 2015
From: Meredith Libeg, Senior Regulatory Health Project Manager -
CDER/OHOP/DOP2
Subject: **NDA 207981** – Taiho Oncology, Inc.
DRISK Review Comments and Information Request

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center Drive, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Our DRISK Reviewer has the following request for information. Please provide your response to me and/or Gina Davis via email by Friday, January 30, 2015, or sooner if possible, and follow that with a formal submission to NDA 207981.

Comments:

1. Please submit as an amendment to your application a copy of your most recent E.U. Risk Management plan and a U.S. risk management plan, if you have one available.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721); or your assigned Regulatory Health Project Manager, Ms. Gina Davis, Gina.Davis@fda.hhs.gov or (301.796.0704).

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/s/

MEREDITH LIBEG
01/16/2015



NDA 207981

NDA ACKNOWLEDGMENT

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center Drive, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Lonsurf (trifluridine and tipiracil hydrochloride), 15 mg and 20 mg tablets

Date of Application: December 19, 2014

Date of Receipt: December 19, 2014

Our Reference Number: NDA 207981

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff (Acting)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
01/09/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 2, 2015
From: Meredith Libeg, Senior Regulatory Health Project Manager -
CDER/OHOP/DOP2
Subject: **NDA 207981** – Taiho Oncology, Inc.
Regulatory Review Comments and Information Request

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center Drive, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Our Regulatory Reviewer has the following request for information. Please provide your response to me via email by Tuesday, January 6, 2015, or sooner if possible, and follow that with a formal submission to NDA 207981.

Comments:

1. We note that you have included all the correspondence originally submitted and received under the cross referenced IND 57674 relating to the agreed initial pediatric study plan (iPSP). Per your agreed iPSP, you state your intent was to submit a full wavier request for pediatric studies for the indication of colorectal cancer; however, we are unable to locate the actual full wavier request (specific to NDA 207981) submitted to the NDA. Please provide the location where this information can be located under the NDA. Alternatively, please submit the full wavier request per the agreed iPSP.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721); or your assigned Regulatory Health Project Manager, Ms. Gina Davis, Gina.Davis@fda.hhs.gov or (301.796.0704).

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/s/

MEREDITH LIBEG
01/02/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 31, 2014
From: Meredith Libeg, Senior Regulatory Health Project Manager -
CDER/OHOP/DOP2
Subject: **NDA 207981** – Taiho Oncology, Inc.
Clinical Review Comments and Information Request

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center Drive, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for “Lonsurf [*Proposed*] (trifluridine/tipiracil).”

Our Clinical Reviewer has the following request for information. Please provide your response to me via email by Tuesday, January 6, 2015, or sooner if possible, and follow that with a formal submission to the NDA.

Clinical Comments:

1. Please provide the address and contact information where the study files for the RECOURSE clinical trial are maintained.

If you have any questions, please feel free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721); or your assigned Regulatory Health Project Manager, Ms. Gina Davis, Gina.Davis@fda.hhs.gov or (301.796.0704).

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/s/

MEREDITH LIBEG
12/31/2014



NDA 207981

ACKNOWLEDGE NDA PRESUBMISSION

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center Drive, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Lonsurf (trifluridine/tipiracil) tablets

Date of Submission: October 16, 2014

Date of Receipt: October 16, 2014

Our Reference Number: NDA 207981

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Monica Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
11/13/2014



IND 57674

MEETING MINUTES

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAS-102.

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2014. The purpose of the meeting was to reach agreement on the content and format of your proposed NDA for TAS-102.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

Final Meeting Minutes
CMC pre-NDA Meeting Minutes
Appendix I – OSI



MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-NDA
Meeting Date and Time: July 31, 2014 from 11:30 AM – 1:00 PM
Meeting Location: CDER WO 22 – Room 1315
Application Number: IND 57674
Product Name: TAS-102; proposed proprietary name - Lonsurf®
Indication: Colorectal Cancer
Sponsor/Applicant Name: Taiho Oncology Inc.

FDA ATTENDEES

Office of Hematology and Oncology Products

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director, DOP 2

Steven Lemery, M.D., M.H.S., Team Lead, DOP 2

Abhilasha Nair, M.D., Medical Officer, DOP 2

Karen Jones, Chief, Project Management Staff, DOP 2

Ruth Maduro, Regulatory Project Manager, DOP 2

Gina Davis, M.T., Regulatory Project Manager, DOP 2

Division of Hematology Oncology Toxicology, (DHOT)

Sachia Khasar, Ph.D., Toxicology Reviewer, DHOT

Office of Clinical Pharmacology

Division Clinical Pharmacology V, (DCP V)

Stacy Shord, Pharm.D, Clinical Pharmacology, Acting Team Lead DCP V

Jun Yang, Ph.D., Clinical Pharmacology Reviewer, DCP V

Office of Biostatistics

Division of Biostatistics V (DB V)

Xiaopeng Jiang, Ph.D., Statistical Reviewer, DB V

Eastern Research Group Attendees

Patrick Liang

SPONSOR ATTENDEES

Manuel Aivado, M.D., Ph.D. Clinical Development and Pharmacovigilance, Taiho Oncology, Inc. (TOI)

Hiroshi Ambe, B.Sc. Clinical Research, TOI

Gigi Atalla, R.Ph. Pharmacovigilance Operations, TOI
Fabio Benedetti, MD Chief Medical Officer, TOI
Eric Benn President and CEO, TOI
Lieselotte Bloss, DVM Regulatory Affairs, TOI
Julie Boisvert, B.Sc. Regulatory Affairs, TOI
Cliff Ding, Ph.D. Statistics, TOI
Hirokazu Mizuguchi, M.S. Clinical Research, TOI
Ken-ichiro Yoshida, Ph.D. Clinical Pharmacology, TOI

1.0 BACKGROUND

On May 15, 2014, Taiho Oncology Inc., (Taiho, formerly Taiho Pharma USA, Inc) requested a pre-NDA meeting to discuss and reach agreement on the content and format of the proposed NDA for the investigational product, TAS-102 (trifluridine/tipiracil hydrochloride). The meeting request granted letter was issued on 4 Jun 2014.

IND 57674 was submitted on 28 Dec 1998, [REDACTED] (b) (4). Taiho submitted a request to inactivate IND 57674 on 15 Jun 2009; that request was granted and IND 57674 was inactivated on 23 Jun 2009.

On 24 Jun 2011, based on the results of a clinical trial conducted in Japan in patients with refractory colorectal cancer, Taiho reactivated IND 57674, and reinitiated clinical development of TAS-102 in the U.S. Taiho subsequently initiated a randomized, placebo-controlled, double-blind trial (TPU-TAS-102-301/ RECURSE) in USA, Europe, Japan, and Australia once the recommended dose was confirmed at 35 mg/m² in the western population. Prior to initiating the TPU-TAS-102-301 trial, a Type B EOP2 meeting was held on 12 Dec 2011 to discuss the trial design. During this meeting, FDA provided comments on issues related to the proposed dose in the US population, QT evaluation plan, clinical pharmacology evaluations, and the statistical analysis plan.

On 25 Oct 2013, the Office of Surveillance and Epidemiology granted Taiho's initial request for the proprietary name Lonsurf (pending resubmission of the request in an NDA).

Taiho stated that TAS-102 was approved in Japan on 24 Mar 2014, 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). Study J003 randomized 170 patients (2:1) with mCRC who progressed or failed to respond to at least two prior chemotherapy regimens that included a fluoropyrimidine, irinotecan, and oxaliplatin. Patients in the experimental arm received TAS-102 at a dose of 35 mg/m²/dose orally twice daily for five days a week (with two days rest) for 2 weeks, followed by a 14 day rest interval (repeated every four weeks). The primary endpoint of the trial was overall survival and the primary endpoint was tested with a one-sided alpha of 0.10. According to results that were described by Taiho and summarized in the 12 Dec 2011 meeting minutes, the study demonstrated that TAS-102 improved OS with a HR for OS of 0.56 with a p-

value of 0.0011 (median difference of 2.4 months). Although positive, the minutes noted baseline differences in prognostic factors between the treatment arms (e.g., 57% men in the treatment arm versus 49% for placebo).

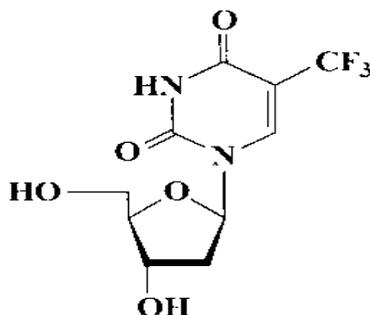
Chemical Name and Structure

TAS-102 (trifluridine/tipiracil hydrochloride), proposed proprietary name Lonsurf[®], is a fixed combination (1:0.5) of α,α,α -trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl- 2,4 (1H,3H)-pyrimidinedione hydrochloride [thymidine phosphorylase inhibitor (TPI)]. TAS-102 is supplied in two strengths: 15 mg white round tablets (containing 15mg FTD and 7.065 mg TPI as the active ingredients) and 20 mg pale-red round tablets (containing 20 mg FTD and 9.42 mg TPI as the active ingredients).

Structural Formula:

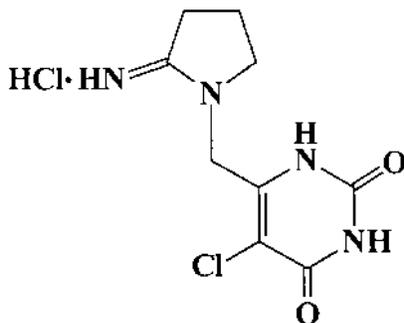
FTD :

α,α,α -trifluorothymidine or 2'-Deoxy-5-(trifluoromethyl)uridine



TPI :

2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1)



Recommended Dose and Route of Administration

Taiho stated that the recommended starting dose in adults, for the immediate-release fill coated tablet, is 35 mg/m²/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).

The current global clinical development program of TAS-102 includes the following eight clinical studies as described in Table 1 below, for which final reports will be submitted as part of the planned NDA.

Study Design	Study Name	Function
Randomized, placebo controlled, double-blind	TPU-TAS-102-301 (RECOURSE)	“Pivotal study”
	J003-10040030 (Japan, phase 2)	
Open-label	J001-10040010 (dose-escalation, Japan, phase 1)	Supportive studies
	J004-10040040 (food effect, Japan, phase 1)	
	TPU-TAS-102-101 (dose escalation, U.S., phase 1)	
	TPU-TAS-102-102 (TPI PK contribution, U.S., phase 1)	
	TPU-TAS-102-103 (QTc, US/UK, phase 1)	
	TPU-TAS-102-104 (bioavailability, U.S., phase 1)	

Taiho stated that the clinical efficacy and safety of TAS-102 were evaluated in a multinational, double-blind, two-arm, parallel-group, randomized study in patients with refractory metastatic colorectal cancer (TPU-TAS-102-301; RECOURSE trial). Randomization in TPU-TAS-102-301 was stratified by KRAS status (wild type vs. mutant), Time since diagnosis of first metastasis (<18 months, ≥18months), and Region (Region 1: Asia [Japan]; Region 2: Western [US, Europe and Australia]). A total 800 eligible patients were randomly assigned in a 2:1 ratio to two treatment arms:

- Experimental: TAS-102 plus best supportive care (BSC) (n=534)
- Control: Placebo plus BSC (n=266)

Treatment was to continue until disease progression or unacceptable treatment-related toxicity.

TAS-102 or placebo was administered at a starting dose of 35 mg/m²/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). Treatment continued until disease progression or unacceptable toxicity.

Taiho stated that in the intent-to-treat (ITT) population, median age was 63 years, 61% of patients were men, 58% were White and 35% were Asian; all patients had a baseline ECOG performance status of 0 or 1.

The primary site of disease was colon for 62% of patients, and rectum for 38% of patients. *KRAS* mutation was present in tumor cells from 51% of patients. The majority of patients (61%) received ≥ 4 prior systemic cancer therapies. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; and all but 1 patient received bevacizumab. All but 2 patients with *KRAS* mutation-negative tumors had received panitumumab or cetuximab.

The primary endpoint was OS. The primary analysis was a stratified log-rank test performed on the ITT population. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of Jan 24, 2014 (4 patients died [REDACTED] (b) (4)). The estimated median OS was 7.1 months for the TAS-102 group versus 5.3 months for the placebo group with a hazard ratio (HR) of 0.68 (95% confidence interval [CI]: 0.58, 0.81), $p < 0.0001$ (stratified log-rank test). The key secondary endpoint was progression-free survival (PFS) as assessed by the investigators. The estimated median PFS was 2.0 months for the TAS-102 group versus 1.7 months for the placebo group with a hazard ratio (HR) of 0.48 (95% CI: 0.41, 0.57), $p < 0.0001$ (stratified log-rank test).

Taiho stated that in the As Treated (AT) safety population [798 patients (533 in TAS-102 group and 265 patients in the placebo group)], the most frequently reported adverse events among patients who received TAS-102 were hematologic events, including neutropenia/neutrophil count decreased, anemia/hemoglobin decreased, and leukopenia/white blood cell count decreased; and gastrointestinal events, including nausea, diarrhea, and vomiting.

1. OBJECTIVE

- The purpose of this meeting is to obtain the Agency's guidance on the content and format of the TAS-102 NDA planned for December 2014.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Preamble: In order to facilitate timely review of the NDA submission, Taiho should consider requesting Fast Track status in order to allow for submission of a rolling NDA. Specifically, FDA would recommend submitting, if ready (and complete) toxicology/non-clinical sections of the NDA prior to submission of other major components of the complete NDA. Please refer to 14 May 2014 FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.

Taiho Oncology's July 29, 2014 response to the Preamble: At your suggestion, we are currently considering several options relevant to fast track designation. One is to submit Module 4 and Module 2 sections 2.4 and 2.6 in September-October. Would this approach to submit partial Module 2 (complete sections 2.4 and 2.6) be acceptable?

We are currently also evaluating the possibility of submitting Module 3, Module 2 section 2.3 and relevant drug master files. What would be the latest acceptable date that would still provide value to the review team?

Discussion during the meeting: Taiho's proposal for submission of the nonclinical module in September-October 2014, if Fast Track designation is granted, is acceptable. FDA agreed that the proposal to submit a complete Module 3, Module 2, section 2.3, and referencing relevant drug master files may be acceptable, however, the contents of the complete sections will need to be discussed with the Office of New Drug Quality Assurance and the Office of Compliance and final agreement will be reached with submission of the schedule of a rolling application. The schedule should be included with the request for Fast Track designation.

Nonclinical

1. Does the Agency agree that the proposed non-clinical studies (pharmacology, safety pharmacology, pharmacokinetics and toxicology studies) would support the approval of TAS-102? (Content of Complete Application - Draft NDA Table of Content is presented in Attachment 3)

FDA Response: The table of nonclinical studies provided in attachment 4 of the meeting package appears sufficient to support the filing of an NDA. Until these studies are reviewed, FDA is unable to comment on the adequacy of the data to support the approval of a marketing application for TAS-102.

Taiho Oncology's July 29, 2014 response to question #1: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

2. The NDA will be prepared in the e-CTD format and submitted via ESG (Electronic Submission Gateway). All non-clinical information will be included in Module 4 except for information from 4 non-clinical studies using human material (Caco-2 cell permeability study, Study of Blood Cell Distribution of FTD and TPI, Plasma metabolite profiling and Search for TPI metabolites in human plasma and urine), which will be included in Section 5.3.2.3. Does the Agency concur with this approach?

FDA Response: No. Please include the information from the four non-clinical studies using human material (Caco-2 cell permeability study, Study of Blood Cell Distribution of FTD and TPI, Plasma metabolite profiling and Search for TPI metabolites in human plasma and urine) in Module 4 rather than Module 5.

Taiho Oncology's July 29, 2014 response to question # 2: We will include the non-clinical studies using human material in Module 4, as recommended. No further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

Clinical

3. The NDA clinical trial package will include the following: two well-designed, placebo-controlled randomized clinical trials (a single, global pivotal Phase 3 clinical trial in metastatic colorectal cancer patients (mCRC) and a supportive phase 2 trial in Japanese mCRC patients) and supportive data from six clinical pharmacology Phase 1 trials in different types of advanced cancer patients (See Attachment 5 for a brief description of the aforementioned trials).

Does the FDA agree that this clinical trial package is adequate for the registration of TAS-102?

FDA Response: Yes, the clinical trial package appears to be adequate to support the review of an NDA for the proposed indication; determination regarding approvability will be made once the application is submitted and reviewed. Note that the submission will be subject to a filing review to assess the adequacy and completeness of the application.

Taiho Oncology's July 29, 2014 response question #3: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

4. Since the demonstration of efficacy will be based on the single phase 3 pivotal trial, Taiho Oncology is not planning to perform a pooled efficacy analysis. Does the Agency concur with our proposal?

FDA Response: Yes, FDA agrees with the proposed plan not to submit a pooled efficacy analysis of Study J003-10040030 and study TPU-TAS-102-301 (RECOURSE) for the reasons included in the meeting package.

Taiho Oncology's July 29, 2014 response to question #4: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

5. Furthermore, the narrative portion of the ISE will be placed in Section 2.7.3 and will be referenced in Module 5, Section 5.3.5.3 (i.e., leaf elements will be provided in both locations). Does the FDA concur with our proposal?

FDA Response: Yes, FDA agrees that that it is reasonable to include the narrative portion of the ISE in Section 2.7.3 of the application with appendices of tables, figures, and datasets of the ISE located in Module 5, as described in FDA Guidance for Industry: Integrated Summaries of Effectiveness and Safety, April 2009. In the application, Taiho

will need to include a clear explanation of where parts of the application are located and provide working cross-links between the two modules. Note that the Summary of Clinical Efficacy is subject to space limitations, and FDA may refuse to file the application if the narrative summary in Section 2.7.3 is longer than 400 pages.

Taiho Oncology's July 29, 2014 response to question #5: Thank you, we will follow the recommendations listed above and FDA Guidance for Industry: *Integrated Summaries of Effectiveness and Safety*, April 2009. No further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

6. In the integrated summary of safety (ISS), Taiho Oncology plans to include 3 ISS data groups. Please refer to Section 6.2 for a brief outline of the presentation of safety information in the ISS. Does the FDA agree with our pooling plan and analysis data sets?

FDA Response: No. FDA recommends that safety data from the proposed ISS Data Group 1 should include safety data from any patient who received the TAS-102 starting dose of 35 mg/m² twice daily. Alternatively, Taiho can submit datasets that include a fourth safety group (maintain the current definition for Group 1) that includes all patients who received the TAS-102 starting dose of 35 mg/m² twice daily (Taiho would not need to generate new (or revised) study reports describing this safety group).

Taiho Oncology's July 29, 2014 response to question #6: Taiho would like to discuss FDA's recommendation to add patients to the ISS irrespective of their cancer type, as long as they received the starting dose of 35mg/m² twice daily. Therefore, we offer the summary below for your further consideration and to foster our discussion.

Using the data from the proposed clinical trial package (8 studies listed in Table 1 of the briefing document), the currently proposed ISS data group 1 comprises a total of 762 patients with mCRC who received the starting dose of 35mg/m² twice daily. Randomized, placebo-controlled trials represent an optimal way to delineate a drug's true safety profile and Taiho's safety data will include data from 2 randomized, placebo-controlled trials, which contribute a total of 646 TAS-102 treated patients (versus a total of 322 placebo-treated patients in those 2 randomized, placebo-controlled trials). Therefore, Taiho considers the proposed safety dataset to be sufficiently large and robust to enable the delineation of the safety profile of TAS-102. Adding patients with a starting dose of 35mg/m² twice daily to the integrated data group 1 irrespective of their underlying disease might introduce qualitative problems without adding quantitative advantages for the following reasons:

- the addition of patients with different cancers bears the risk of confounding the resulting safety profile with safety information that is primarily driven by the different cancer types; and

- the potential quantitative advantage of adding more patients with a starting dose of 35mg/m² twice daily irrespective of their underlying cancers is limited because in our proposed clinical trial package, there were only 68 additional patients who met this criterion. This would represent an additional 9% of patients, only;

Therefore, Taiho proposes to keep the ISS data groups in their current form, i.e. avoiding the integration of safety data for patients with different cancer indications into one single dataset.

Discussion during the meeting: In response to FDA's request for clarification, Taiho stated that there will be two datasets containing data from patients with colorectal cancer (CRC) in CDISC format, and a third dataset containing SAE information in patients with CRC or other diagnoses, which is not in CDISC. FDA agreed that this information would be sufficient to support review but requested that the third dataset include demographic information (e.g. age, gender, race and weight or body mass), dosing information, and the primary cancer diagnosis. Taiho will attempt to provide a flag in the datasets that identifies any patient who received the dose of 35 mg/m² twice daily.

7. Taiho Oncology is proposing a safety (SAEs) cutoff date of July 24, 2014 for the inclusion in the NDA that is planned for mid-December 2014. All SAEs reported for TAS-102 prior to the SAE cutoff, regardless of the TAS-102 dose or cancer type, will be reported in the NDA using the Pharmacovigilance database.

Does the Agency agree with our proposal?

FDA Response: Yes, FDA agrees with the proposed cutoff date of July 24, 2014, provided that the NDA is planned to be submitted mid-December 2014. FDA recommends a data cut-off for submission of safety data of no more than 6 months prior to the submission of the NDA.

Taiho Oncology's July 29, 2014 response to question #7: Thank you, no further discussion is necessary at the meeting

Discussion during the meeting: No discussion occurred.

8. At the time of submission, Taiho Oncology intends to request a priority review designation based mCRC being a serious condition for which TAS-102 provides significant improvements of safety or effectiveness of TAS-102 over placebo for the treatment of mCRC. If granted, we propose a 120-day safety-cutoff date of January 19, 2015 and submission date of March 19, 2015 for the 120-day safety update report. Furthermore, the proposed 120-day safety update report content is summarized in Section 6.2. Does the FDA agree with the proposed content and cut-off date?

FDA Response: FDA agrees with the proposed safety update cut-off date. However *if* the NDA receives priority review; however, FDA recommends submission of the safety update 90 days after submission of the NDA.

FDA does not agree with the proposed content. As stated in 21 CFR 314, an applicant shall update periodically its pending application with new safety information learned about the drug that may *reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling*. Therefore, FDA does not agree with the plan to submit all AEs reported from the RECURSE study between 31 Jan 2014 and the proposed safety update. Because a complete safety database (through the data cut-off date) is expected at the time of the initial NDA submission, additional safety data in the safety update should be minimal (limited to deaths and serious adverse events).

Note that FDA's determination regarding priority review is assigned to a NDA for a drug that treats serious conditions and which provide significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies (i.e., not on a significant improvement *over placebo*).

Taiho Oncology's July 29, 2014 response to question #8: Taiho agrees with FDA's recommendation and will not update the AE data from the RECURSE study in the 120-day safety update report. Taiho would like to discuss FDA's comment regarding priority review determination requirements. Taiho plans to request priority review for TAS-102 at the time of the NDA submission. The planned original NDA for TAS-102 will represent an application for a drug that treats a serious condition, and, if approved, would provide a significant improvement in safety and effectiveness.

Taiho considers metastatic colorectal cancer (mCRC) to meet the definition (and qualifying criteria) of a serious condition as stipulated in section III.A (section IV) of the FDA Guidance for Industry entitled "Expedited Programs for Serious Conditions – Drugs and Biologics" (May 2014). Furthermore, TAS-102 demonstrates the potential to be a significant improvement in effectiveness of the treatment of mCRC, as evidenced by the following:

The pivotal RECURSE study demonstrated a clinically meaningful and statistically significant improvement in OS for patients with mCRC (Hazard Ratio = 0.68). These patients had to have failed or had to be intolerant to ALL therapies approved at the time of the beginning of the RECURSE study, which started enrolment June 17, 2012. These therapies include a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR antibody (if KRAS wild-type).

Of note, on September 27, 2012, FDA approved Stivarga for the same patient population that was studied in RECURSE. In a pre-specified analysis of the RECURSE data, Taiho examined the outcome of mCRC patients who received treatment with Stivarga prior to randomization to TAS-102 or placebo. Eighteen percent (18%, 144/800) of all randomized patients had received prior treatment with Stivarga (91 TAS-102 patients and 53 placebo patients had received prior treatment with Stivarga), all in the Western region due to availability of regulatory approvals. The same clinical benefit was observed irrespective of prior treatment with regorafenib, as evidenced by the OS Hazard Ratio of 0.69 for both comparisons.

In addition, though Stivarga does provide a treatment option for patients in the same refractory metastatic CRC setting as was evaluated in RECURSE for TAS-102, there still remains an urgent need for other effective treatment options. To note, a significant number of patients in the Phase III trial with regorafenib in refractory metastatic CRC were reported to have progressed in or within 2 months of treatment. For these patients, currently, there are no other effective treatment options.

Does the FDA agree that this rationale will support priority review?

Discussion during the meeting: FDA stated that Taiho's proposed approach for supporting a request for priority review designation appeared appropriate. Taiho agreed to submit the safety update at day 90 regardless of the review designation.

9. Taiho Oncology plans to include the individual case report forms and the Clinical Study Report (CSR) narratives for all patients who had a serious adverse event, who died within 30 days after the last dose of study medication, or who discontinued from study due to an adverse event. Does the Agency agree with our proposal?

FDA Response: FDA agrees with the plan regarding the submission of CRFs based on the criteria outlined above in the NDA; however, please be prepared to submit other CRFs promptly (e.g., within 1 week) upon request (including CRFs from legacy studies as was defined in the briefing package). Regarding patient narratives, please also provide patient narratives (from Study TPU-TAS-102-301) for those patients who prematurely terminated study drug for the following reasons: "other", lost to follow-up, physician decision, or subject decision.

Narratives summaries should contain the following components:

- subject age and gender
- signs and symptoms related to the adverse event being discussed
- an assessment of the relationship of exposure duration to the development of the adverse event
- pertinent medical history
- concomitant medications with start dates relative to the adverse event
- pertinent physical exam findings
- pertinent test results (for example: lab data, ECG data, biopsy data)
- discussion of the diagnosis as supported by available clinical data
- a list of the differential diagnoses, for events without a definitive diagnosis
- treatment provided
- re-challenge and de-challenge results (if performed)
- outcomes and follow-up information

- an informed discussion of the case, allowing a better understanding of what the subject experienced.

Taiho Oncology's July 29, 2014 response question #9: TPU-TAS-102-301 patient narratives from patients who prematurely terminated study drug for the following reasons: "other", lost to follow-up, physician decision, or subject decision will be added to the CSR. All patient narratives will include the information recommended above.

Discussion during the meeting: No discussion occurred.

10. Taiho Oncology will summarize the available information on the major elimination pathways as well as the metabolism of TAS-102 components in sections 2.4 (non-clinical overview) and 2.7.2 (clinical summary) of the NDA. In addition, Taiho Oncology is conducting a mass balance study (TPU-TAS-102-108) to confirm the available mass balance and metabolism information in humans. The CSR is anticipated to be issued in 2Q2015. Please refer to Attachment 2 for additional information. Does the agency agree with our approach and timelines?

FDA Response: Yes, FDA agrees. See additional clinical pharmacology comments.

Taiho Oncology's July 29, 2014 response question #10: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

11. Taiho Oncology is planning to initiate studies of TAS-102 in patients with hepatic impairment (TO-TAS-102-106) and renal impairment (TO-TAS-102-107) in 4Q 2014. The initial NDA will include a population PK analysis that will assess the impact of renal and hepatic impairment in our current studies. Does the Agency agree with our approach?

FDA Response: Yes, FDA agrees. See additional clinical pharmacology comments.

Taiho Oncology's July 29, 2014 response question #11: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

12. Taiho Oncology will provide the certification and disclosure statements only for investigators who participated in the pivotal Phase 3 study (TPU-TAS-102-301/RECOURSE). Does the Agency agree?

FDA Response: No, FDA does not agree with this proposal. Provide certification and disclosure statements for all investigators in any of the "covered clinical studies" that Taiho intends to submit to support the safety and efficacy of TAS-102 for the proposed indication. Specifically, FDA believes that J003-10040030 is a covered study as it provides data supporting the treatment effect claimed based on the TPU-TAS-102-

301 trial. For a detailed definition of what constitutes a covered clinical study please refer to 21CFR54.2(e) or the “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators”
<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf>.

Provide justification in the NDA for studies that Taiho believes is exempt from this requirement. FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)).

Taiho Oncology’s July 29, 2014 response question #12: Study J003-10040030 was not conducted under the IND. Retrospectively; we have contacted each site, and collected the financial disclosure (FD) of the principal investigator (PI). Of note, the organizational structure in Japan is such that the ultimate responsibility over safety and efficacy information resides with the PI, and accordingly all CRFs were in fact signed by the responsible PI. Therefore, FD was collected only from those responsible PIs and Taiho considers this to be in line with FDA “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators”.

As suggested, we now consider that RECOURSE and J003-10040030 meet the “covered study” definition. Does the FDA have further comments?

Discussion during the meeting: FDA stated that Taiho’s approach is acceptable.

Electronic Submission

13. Supportive SAS programs (all analysis dataset programs, all table programs that include inferential statistics, and all figure programs that include survival or inferential statistics) will be provided for the following studies: TPU-TAS-102-101, TPU-TAS-102-102, TPUTAS-102-103, TPU-TAS-102-104, TPU-TAS-102-301, J001-10040010, J003-10040030 and J004-10040040, as well as the ISS. Additional SAS programs that will allow FDA to execute these programs will be provided for the Phase 3 study (TPU-TAS-102-301) and for the ISS. Does the Agency agree with our proposal?

FDA Response: The proposal is acceptable. However, the SAS programs that are provided in the NDA submission should be stand-alone programs, e.g. the programs can be used to reproduce the major efficacy and safety results in the Clinical Study Report and the proposed labeling. Also please provide a reviewer’s guide that provides descriptions of analyses, the names of datasets and variables used in those SAS programs.

Taiho Oncology's July 29, 2014 response to question #13: We will follow the recommendation listed above; no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

14. Based on the preliminary safety profile of TAS-102, we believe that the potential risks will be adequately addressed through labeling and that a REMS will not be necessary. Does the Agency concur with this approach?

FDA Response: Yes, on preliminary evaluation and based on the data provided in the meeting package, a REMS will not be required for filing. However, a formal determination on the need for a REMS will be determined during the review of the NDA.

Taiho Oncology's July 29, 2014 response to question #14: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

15. As proposed by Taiho Oncology (pre-NDA CMC Meeting Request dated 31 October 2013, Serial No. 0217) and accepted by the FDA (refer to Meeting Preliminary Comment letter dated 27 November 2013), Taiho Oncology will submit 12 months LTSS (long-term stability study) data for all three primary batches within 30 days from the original NDA submission. The original NDA will include 9 months long-term and 6 months accelerated stability data for three primary batches of drug product. Does that FDA have any additional comment?

FDA Response: FDA has no additional comments.

Taiho Oncology's July 29, 2014 response to question #15: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

Additional Comments

Clinical

16. FDA has the following preliminary comments regarding the proposed labeling in Attachment 6 of the briefing package. Lack of comment does not necessarily indicate FDA agreement with the Section. Prior to submitting a proposed label in the NDA, please ensure that the label conforms to the requirements set forth in the Physician Labeling Rule (see general comment below). To ensure timely review of the NDA, FDA strongly recommends following the labeling Guidance documents contained in the following web-link

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments on those additional comments with the exceptions of the following:

- Indications and Usage: Do not use promotional terms (b) (4)
- Recommended Dose: The Dosage and Administration Section appears to be overly complicated and thus likely to result in medication errors. Provide justification that this level of complexity (e.g., multiple lengthy tables) is necessary to ensure safe use and that in the clinical trial experience these recommendations were followed consistently and accurately.

Taiho Oncology's July 29, 2014 response to additional comment #16 regarding the Recommended Dose under the "Dosage and Administration Section" of the proposed label: We would like to better understand the FDA's statement that the proposed recommended dose section is "overly complicated".

Discussion during the meeting: FDA requested that dosing information be provided in a clear, concise format; FDA suggested describing the recommended dose in text as an option rather than in the proposed (b) (4) format. Taiho will explore dosing strategies that are less complex than those used in the clinical trials and will propose these dosing strategies in the label if supported by clinical data.

- Contraindication: Refer to the Guidance document at the following weblink: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. Unless, you have data supporting the proposed (b) (4) contraindication, remove this contraindication from the label.
- Warnings: Based on the class of drugs, include a Warning notifying prescribers of the increased risk of severe toxicity in patients with known dihydropyrimidine dehydrogenase deficiency (DPD). Alternatively, provide data that the metabolism of trifluridine bypasses the DPD pathway.

Also, in order to support a Warning, provide data justifying (b) (4)

Taiho Oncology's July 29, 2014 response to additional comment #16 regarding the "Warnings and Precautions" Section of the proposed label: Taiho does not intend to provide a warning about DPD deficiencies because the primary enzyme involved in the catabolism of FTD is thymidine phosphorylase, and the primary enzyme involved in the activation of FTD is thymidine kinase 1. In contrast, DPD is not involved in the activation or in the catabolism of FTD. Therefore, DPD deficiency will not affect either the safety or efficacy of TAS-102.

Discussion during the meeting: In regards to the Warning regarding DPD deficiency, FDA acknowledged Taiho's response and agreed that a Warning does not appear necessary based on the response provided. Taiho agreed to provide the information supporting the metabolism of TAS-102 in the NDA to support the omission of a Warning based on DPD.

- Overdosage: Revise this Section based on human data if such data exists. This section should not include general information (b) (4)
- Mechanism of Action: Remove all statements that imply comparative efficacy to other drugs ((b) (4) This section should describe the mechanism of action and not make promotional claims.

17. As stated in the 12 Dec 2011 meeting minutes for the Type B meeting held between Taiho and FDA, Taiho will need to provide adequate justification that TPI is a necessary component of TAS-102 and why trifluridine alone (e.g., at a higher dose or more frequent schedule) is not sufficient to provide the proposed treatment effect. In addition to providing pharmacokinetic data to support this justification, FDA recommends that Taiho provide a discussion regarding the practicality (or lack thereof) if a patient were required to take trifluridine alone (without TPI).

Taiho Oncology's July 29, 2014 response to additional comment #17: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

18. FDA acknowledges that Taiho will submit datasets in CDISC format using Implementation Guide 3.1.2. Although FDA agrees that it is acceptable to use this version of CDISC for submission of datasets, FDA requests that Taiho include additional variables in the demographics dataset (i.e., variables included in more recent STDM versions) in order to facilitate timely review of the data. These variables include: actual treatment arm (i.e., actual treatment received), death flag, date of death, date of informed consent, and date of first exposure to study drug.

Taiho Oncology's July 29, 2014 response to additional comment #18: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

19. The briefing package contains the statement: "the analysis datasets will generally be modeled in accordance with the Analysis Data Model version 2.1: Implementation Guide version 1.0 but will deviate from these guidance documents where necessary to

accurately represent the data as it was collected and analyzed.” In the NDA, please describe deviations from the guidance documents to ensure timely review of the data.

Taiho Oncology’s July 29, 2014 response to additional comment #19: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

Clinical Pharmacology

Please address the following clinical pharmacology related questions in the NDA submission:

20. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

Taiho Oncology’s July 29, 2014 response to additional comment #20: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

21. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
22. What are the exposure-response relationships (dose-response, exposure-response) for safety?

Taiho Oncology’s July 29, 2014 response to additional comment # 21 & 22: For safety, Taiho will provide information about the exposure-response relationship in the NDA based on the results of J001-10040010 (n=21). In addition, we are preparing an exposure-response relationship analysis for efficacy and safety based on RECOURSE results, and this report is anticipated to be available in March 2015.

Discussion during the meeting: FDA stated that Taiho should submit all available population pharmacokinetic and exposure-response analyses at the time of the submission of the original NDA.

FDA stated that under the PDUFA V Program, FDA cannot agree to accept a major component, e.g., the exposure-response analyses for Study RECOURSE, as a late submission. Taiho will need to provide adequate justification as to why the original NDA submission is complete without these analyses. FDA further stated that if Taiho does not

plan to submit the exposure-response analyses for Study RECOURSE with the original NDA, Taiho should propose a postmarketing requirement (PMR) or postmarketing commitment (PMC) to submit these analyses, including milestones, to the FDA for review within the original NDA submission.

23. How is the QT prolongation potential of TAS-102 assessed? What are the conclusions and proposed labeling description?

Taiho Oncology's July 29, 2014 response to additional comment #23: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

24. What are the characteristics of absorption, distribution, metabolism and excretion of TAS-102?

Taiho Oncology's July 29, 2014 response to additional comment #24: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

25. What are the effects of food on the bioavailability of TAS-102 and dosing recommendation with regard to meals or meal types?

Taiho Oncology's July 29, 2014 response to additional comment #25: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

26. What influence do the intrinsic factors (as listed below but not limited to) have on TAS-102 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?

- a. gender
- b. race
- c. weight
- d. disease
- e. genetic polymorphism
- f. hepatic impairment
- g. renal impairment

Taiho Oncology's July 29, 2014 response to additional comment #26: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments.

Discussion during the meeting: No discussion occurred.

27. What influence do the extrinsic factors (as listed below but not limited to) have on TAS-102 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

Taiho Oncology's July 29, 2014 response to additional comment #27: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

In addition, please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

28. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Taiho Oncology's July 29, 2014 response to additional comment #28: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

29. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The subject's ID number in PK datasets should be consistent to those in datasets submitted for clinical review.

Taiho Oncology's July 29, 2014 response to additional comment #29: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

30. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Taiho Oncology's July 29, 2014 response to additional comment #30: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

31. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

Taiho Oncology's July 29, 2014 response to additional comment #31: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

32. Provide a table listing of patients with renal or hepatic impairment who have received TAS-102, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Taiho Oncology's July 29, 2014 response to additional comment # 32: We will prepare a table as requested above. Could the FDA suggest the preferred location of this table in the eCTD? Would FDA be willing to review a mock output after the meeting for comments? If feasible, could the FDA please indicate to whom this table should be submitted for review?

Discussion during the meeting: FDA stated that the table, and its associated transport and programming files, should be submitted in Module 5: Clinical Study Reports under Section [5.3.5.3 Reports of analyses of data from more than one study](#). FDA stated that a mock output report would not be reviewed and therefore, Taiho should not submit the report.

33. Submit the following datasets to support the population PK analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - Description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)
- Model development decision tree and/or table which gives an overview of modeling steps

For the population analysis reports, submit

- Standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information

Taiho Oncology's July 29, 2014 response to additional comment #33: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

34. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for TAS-102 and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

Taiho Oncology's July 29, 2014 response to additional comment #34: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

35. Submit the following items for QTc study/assessment
- Copy of the QT/QTc study protocol
 - Copy of the Investigator's Brochure
 - Annotated CRF
 - Define file which describes the contents of the electronic data sets
 - Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - Completed Highlights of Clinical Pharmacology Table

Taiho Oncology's July 29, 2014 response to additional comment #35: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- FDA and Taiho reached general agreement on the contents and format of the all modules of the NDA.
- FDA and Taiho reached agreement on the content of a complete application. FDA agreed that the following minor component may be submitted no later than 30 calendar days:
 - 12 months stability data for all three primary batches.
- The application will include comprehensive and readily available lists of all clinical and manufacturing sites. Taiho stated that the OSI datasets limited to the RECURSE Study will be submitted to the IND or NDA prior to submission of the last module of the NDA (i.e., the complete application).
- Based on the preliminary safety profile of TAS-102 provided by Taiho in the meeting package, a REMS will not be required for filing, however, a formal determination on the need for a REMS will be determined during the review of the NDA.
- FDA recommended that Taiho submit a request for Fast Track designation that includes the schedule for a rolling NDA submission.
- On November 27, 2013 the Office of New Drug Quality Assessment issued preliminary comments to Taiho Oncology, Inc., (formerly known as Taiho Pharma USA, Inc.) in response to the questions contained in the October 31, 2013 briefing document in preparation for the December 5, 2013 face to face meeting with Taiho Oncology.

Taiho Oncology reviewed the preliminary comments and elected to cancel the December 5, 2013 face to face meeting as no further explanation or clarification of the preliminary responses was required.

The preliminary comments issued on November 27, 2013 stand as the final pre-NDA CMC meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities responsible for the commercial process, associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

In addition to commercial manufacturing facilities, please include all manufacturing facilities where batches were made to support the application (if they differ from facilities intended for commercial manufacturing). Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

THE OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

Appendix I contains information that will facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments. The Agency strongly encourages Taiho Oncology to formally submit the information noted in Appendix I (Item I and Item II) to the IND prior to submission of the NDA.



IND 57674

MEETING PRELIMINARY COMMENTS

Taiho Pharm USA, Inc.
Attention: Daljit K. Gill, MD
Global Senior Director, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Gill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAS-102.

We also refer to your, correspondence, received September 10, 2013, requesting a meeting to discuss Taiho's plans to accelerate the preparation of CMC sections of their application and to follow up on items discussed at the CMC End of Phase 2 meeting on November 29, 2011.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA, CMC

Meeting Date and Time: December 5, 2013; 11:00AM-12:00PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 57674
Product Name: TAS-102
Indication: Treatment of Malignant Solid Tumors
Sponsor/Applicant Name: Taiho Pharm USA, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 5, 2013; 11:00AM-12:00PM (EST) and the FDA White Oak Campus between Taiho Pharm USA, Inc. and the Division of New Drug Quality Assessment I. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On September 10, 2013, the Agency received a Type B meeting request from Taiho Pharm USA, Inc. The purpose of the meeting is to discuss Taiho's plans to accelerate the preparation of CMC sections of their application and to follow up on items discussed at the CMC End of Phase 2 meeting on November 29, 2011. The Meeting Packages were received on November 1, 2013.

2.0 DISCUSSION

Question 1 Part 1:

Is Taiho's proposal for the amount of stability data in the NDA (9 months long-term, 6 months accelerated stability data) as well as the bracketing design for the LTSS and accelerated stability data acceptable?

FDA Response to Question 1 Part 1:

Your proposed approach of submitting 9 months LTSS and 6 months accelerated stability data at initial NDA submission followed by 12 months stability data within 30 days of the NDA submission appears acceptable. It is expected that you will provide 12 months of LTSS data for all three primary stability batches within the 30 days from the NDA submission. Your proposed bracketing design for the LTSS and accelerated stability study appears reasonable.

Question 1 Part 2:

If it is necessary to have 12 months stability data at the time of initial NDA submission, Taiho could include 12 months stability data from a process qualification batch (15 and 20 mg tablets) as supportive data in the NDA, rather than delaying the NDA submission in order to include the 12 months stability data from the LTSS batches. Is this proposal acceptable to the Agency?

FDA Response to Question 1 Part 2:

Refer to the response to Part 1 of Question 1.

Question 1 Part 3:

The 3 batches for long-term stability study (LTSS) were manufactured and packaged at Taiho in Japan. The bulk tablets used for LTSS were manufactured at full production scale but the packaging operations for the LTSS batches were not done at full production scale. The bulk tablets for commercialization in the US will be manufactured at Taiho in Japan using the validated manufacturing process, and will be shipped to a packaging site selected for the US market, prior to release testing and distribution to the market. As part of the registration stability study (LTSS), Taiho is conducting bulk stability study including shipping studies, and freeze/thaw studies to support the shipment of bulk tablets from Japan to the packaging site selected for the US market. The commercial packager for the US will be identified during the first half of 2014 and they will use packaging components identical to those used in the LTSS to package the commercial supplies. Taiho will place one batch of each product strength (15 and 20 mg) packaged in the commercial packaging container closure on routine stability annually after approval.

Does the Agency agree with Taiho's overall strategy for the stability program?

FDA Response to Question 1 Part 3:

Your proposal to place one batch of each product strength (15 and 20 mg) packaged in the commercial container closure system on annual stability program post approval is acceptable. It is recommended that you select the annual stability batches using the lowest

count configuration (20 counts) for each strength (15 mg and 20 mg) of the drug product for your annual stability testing program.

Question 2 Part 1:

Manufacturing Process Validation - Taiho plans to do manufacturing process validation in two stages. Manufacturing process validation up to the bulk tablets has been completed recently at Taiho in Japan. The packaging process validation will be at a later date using future batches of bulk tablets. Taiho is currently in the process of selecting a packaging vendor for US commercial supplies. Packaging process validation will be done at the selected packaging vendor using the bulk tablets manufactured at full production scale according to the validated manufacturing process at Taiho in Japan.

Does the Agency agree with this two stage Manufacturing Process Validation strategy?

FDA Response to Question 2 Part 1:

The proposed process validation approach to be performed by two facilities for bulk manufacturing and packaging appears reasonable if you intend for the commercial process to be manufactured this way. However, the Agency cannot reach a conclusion on the acceptability of your process validation activities until the actual protocols, acceptance criteria and study outcomes are evaluated during an inspection.

In general, it is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. The number of lots for each strength included in a validation plan is not a performance criterion. FDA does not approve process validation plan, protocols, or specific batches used in process validation studies.

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Question 2 Part 2:

Batch Record - Does the Agency concur with a strategy to include executed batch records for bulk tablets of a full production scale lot of each strength of TAS-102 (15 and 20 mg) in the regional section of the NDA at submission and provide executed packaging batch records from the packaging validation runs at the commercial packaging site post approval?

FDA to Question 2 Part 2:

Your approach appears acceptable.

Question 2 Part 3:

Commercial Strategy for US - The bulk tablets for commercialization in US will be manufactured at Taiho in Japan, and shipped to a packaging site selected for the US market for commercial packaging/distribution. As part of the registration stability study (LTSS), Taiho is conducting bulk stability study including shipping studies, and freeze/thaw studies to support the shipment of bulk tablets from Japan to the packaging site selected for the US market, prior to release testing and distribution to the US market.

Does the Agency agree with Taiho's commercial strategy?

FDA to Question 2 Part 3:

Your proposed plan for the shipping and freeze/thaw studies appears reasonable. The hold time study, shipping validation and freeze/thaw study should be representative of the conditions that the commercial product will experience.

Question 3:

Does the Agency agree with Taiho's strategy of using a DMF for inclusion of TPI drug substance information in the NDA?

FDA Response to Question 3:

You approach appears acceptable.

Question 4:

Does the Agency agree with the proposed acceptance criteria for related substances in (b) (4), a starting material in TPI drug substance?

FDA Response to Question 4:

The proposed acceptance criteria for related substances in (b) (4) appear reasonable based on the information submitted in the meeting package dated October 31, 2013. However, determination of acceptability of the acceptance criteria for related substances in (b) (4) will be made during the NDA review when all CMC information and relevant data have been evaluated.

Although the information provided appears to show that it is reasonable to designate (b) (4) as a starting material in TPI drug substance, final determination of the acceptability of the proposed starting materials for TP1 drug substance will be made during the NDA review. You should also provide the following additional information in your NDA to support the designation of the starting materials:

- **Appropriate change controls are in place for the manufacturing of TP1**
- **Validated analytical methods to detect and quantitate impurities in the drug substance, intermediates, and the proposed starting materials.**
- **Impurity profile data from all available batches of the proposed starting material, (b) (4), and their corresponding intermediate and drug substance batch analysis data.**

Question 5:

Does the Agency agree with the proposed specifications for TPI starting material (b) (4)?

FDA Response to Question 5:

The proposed specifications for (b) (4) appear reasonable based on the information submitted in the meeting package dated October 31, 2013. However, determination of acceptability of the proposed specifications for (b) (4) will be made at the NDA review when all CMC information and relevant data have been evaluated. Also refer to answers to Question 4.

Additional Comment:

Please let us know the proposed date that you are planning to submit your NDA.

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JEWELL D MARTIN
11/27/2013

ALI H AL HAKIM
11/27/2013

Appendix I

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

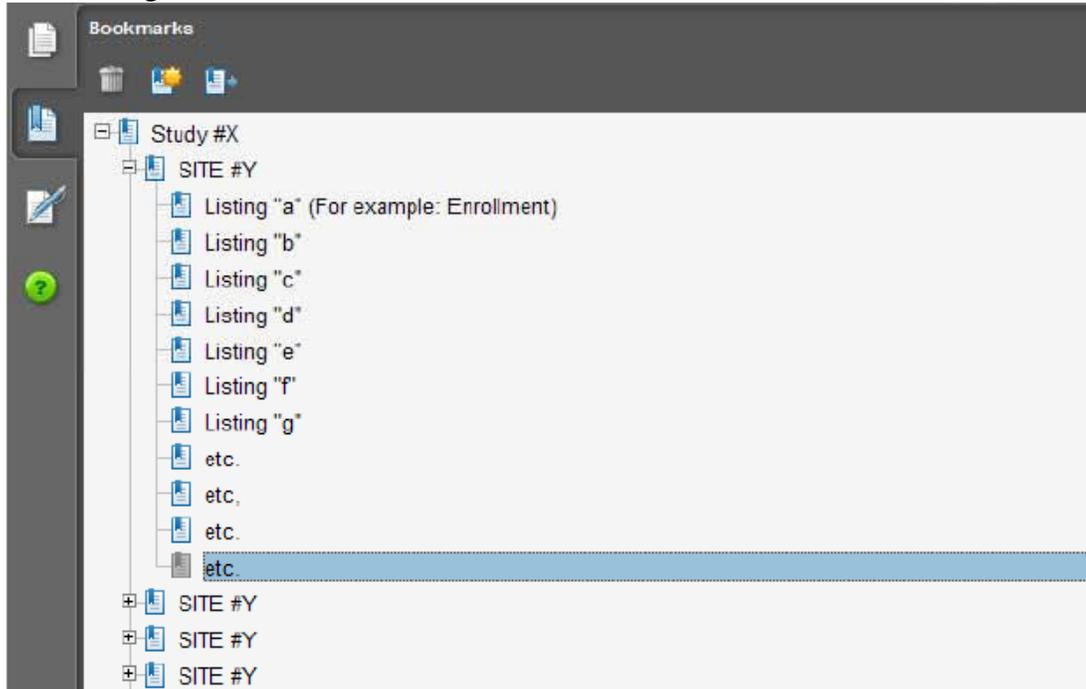
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

- j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL



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
08/21/2014



IND 57674

MEETING PRELIMINARY COMMENTS

Taiho Pharm USA, Inc.
Attention: Daljit K. Gill, MD
Global Senior Director, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Gill:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAS-102.

We also refer to your, correspondence, received September 10, 2013, requesting a meeting to discuss Taiho's plans to accelerate the preparation of CMC sections of their application and to follow up on items discussed at the CMC End of Phase 2 meeting on November 29, 2011.

Our preliminary responses to your meeting questions are enclosed.

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If you have any questions, call me, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Jewell D. Martin, MA, MBA, PMP
Regulatory Project Manager for Product Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA, CMC

Meeting Date and Time: December 5, 2013; 11:00AM-12:00PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Application Number: IND 57674
Product Name: TAS-102
Indication: Treatment of Malignant Solid Tumors
Sponsor/Applicant Name: Taiho Pharm USA, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 5, 2013; 11:00AM-12:00PM (EST) and the FDA White Oak Campus between Taiho Pharm USA, Inc. and the Division of New Drug Quality Assessment I. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

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2.0 DISCUSSION

Question 1 Part 1:

Is Taiho's proposal for the amount of stability data in the NDA (9months long-term, 6 months accelerated stability data) as well as the bracketing design for the LTSS and accelerated stability data acceptable?

FDA Response to Question 1 Part 1:

Your proposed approach of submitting 9 months LTSS and 6 months accelerated stability data at initial NDA submission followed by 12 months stability data within 30 days of the NDA submission appears acceptable. It is expected that you will provide 12 months of LTSS data for all three primary stability batches within the 30 days from the NDA submission. Your proposed bracketing design for the LTSS and accelerated stability study appears reasonable.

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If it is necessary to have 12 months stability data at the time of initial NDA submission, Taiho could include 12 months stability data from a process qualification batch (15 and 20 mg tablets) as supportive data in the NDA, rather than delaying the NDA submission in order to include the 12 months stability data from the LTSS batches. Is this proposal acceptable to the Agency?

FDA Response to Question 1 Part 2:

Refer to the response to Part 1 of Question 1.

Question 1 Part 3:

The 3 batches for long-term stability study (LTSS) were manufactured and packaged at Taiho in Japan. The bulk tablets used for LTSS were manufactured at full production scale but the packaging operations for the LTSS batches were not done at full production scale. The bulk tablets for commercialization in the US will be manufactured at Taiho in Japan using the validated manufacturing process, and will be shipped to a packaging site selected for the US market, prior to release testing and distribution to the market. As part of the registration stability study (LTSS), Taiho is conducting bulk stability study including shipping studies, and freeze/thaw studies to support the shipment of bulk tablets from Japan to the packaging site selected for the US market. The commercial packager for the US will be identified during the first half of 2014 and they will use packaging components identical to those used in the LTSS to package the commercial supplies. Taiho will place one batch of each product strength (15 and 20 mg) packaged in the commercial packaging container closure on routine stability annually after approval.

Does the Agency agree with Taiho's overall strategy for the stability program?

FDA Response to Question 1 Part 3:

Your proposal to place one batch of each product strength (15 and 20 mg) packaged in the commercial container closure system on annual stability program post approval is acceptable. It is recommended that you select the annual stability batches using the lowest

count configuration (20 counts) for each strength (15 mg and 20 mg) of the drug product for your annual stability testing program.

Question 2 Part 1:

Manufacturing Process Validation - Taiho plans to do manufacturing process validation in two stages. Manufacturing process validation up to the bulk tablets has been completed recently at Taiho in Japan. The packaging process validation will be at a later date using future batches of bulk tablets. Taiho is currently in the process of selecting a packaging vendor for US commercial supplies. Packaging process validation will be done at the selected packaging vendor using the bulk tablets manufactured at full production scale according to the validated manufacturing process at Taiho in Japan.

Does the Agency agree with this two stage Manufacturing Process Validation strategy?

FDA Response to Question 2 Part 1:

The proposed process validation approach to be performed by two facilities for bulk manufacturing and packaging appears reasonable if you intend for the commercial process to be manufactured this way. However, the Agency cannot reach a conclusion on the acceptability of your process validation activities until the actual protocols, acceptance criteria and study outcomes are evaluated during an inspection.

In general, it is the company's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. The number of lots for each strength included in a validation plan is not a performance criterion. FDA does not approve process validation plan, protocols, or specific batches used in process validation studies.

FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process.

Please find more information in the Guidance for Industry, *Process Validation: General Principles and Practices* (January 2011).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>

Question 2 Part 2:

Batch Record - Does the Agency concur with a strategy to include executed batch records for bulk tablets of a full production scale lot of each strength of TAS-102 (15 and 20 mg) in the regional section of the NDA at submission and provide executed packaging batch records from the packaging validation runs at the commercial packaging site post approval?

FDA to Question 2 Part 2:

Your approach appears acceptable.

Question 2 Part 3:

Commercial Strategy for US - The bulk tablets for commercialization in US will be manufactured at Taiho in Japan, and shipped to a packaging site selected for the US market for commercial packaging/distribution. As part of the registration stability study (LTSS), Taiho is conducting bulk stability study including shipping studies, and freeze/thaw studies to support the shipment of bulk tablets from Japan to the packaging site selected for the US market, prior to release testing and distribution to the US market.

Does the Agency agree with Taiho's commercial strategy?

FDA to Question 2 Part 3:

Your proposed plan for the shipping and freeze/thaw studies appears reasonable. The hold time study, shipping validation and freeze/thaw study should be representative of the conditions that the commercial product will experience.

Question 3:

Does the Agency agree with Taiho's strategy of using a DMF for inclusion of TPI drug substance information in the NDA?

FDA Response to Question 3:

Your approach appears acceptable.

Question 4:

Does the Agency agree with the proposed acceptance criteria for related substances in (b) (4) a starting material in TPI drug substance?

FDA Response to Question 4:

The proposed acceptance criteria for related substances in (b) (4) appear reasonable based on the information submitted in the meeting package dated October 31, 2013. However, determination of acceptability of the acceptance criteria for related substances in (b) (4) will be made during the NDA review when all CMC information and relevant data have been evaluated.

Although the information provided appears to show that it is reasonable to designate (b) (4) as a starting material in TPI drug substance, final determination of the acceptability of the proposed starting materials for TP1 drug substance will be made during the NDA review. You should also provide the following additional information in your NDA to support the designation of the starting materials:

- Appropriate change controls are in place for the manufacturing of TP1
- Validated analytical methods to detect and quantitate impurities in the drug substance, intermediates, and the proposed starting materials.
- Impurity profile data from all available batches of the proposed starting material, (b) (4) and their corresponding intermediate and drug substance batch analysis data.

Question 5:

Does the Agency agree with the proposed specifications for TPI starting material (b) (4)?

FDA Response to Question 5:

The proposed specifications for (b) (4) appear reasonable based on the information submitted in the meeting package dated October 31, 2013. However, determination of acceptability of the proposed specifications for (b) (4) will be made at the NDA review when all CMC information and relevant data have been evaluated. Also refer to answers to Question 4.

Additional Comment:

Please let us know the proposed date that you are planning to submit your NDA.

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JEWELL D MARTIN
11/27/2013

ALI H AL HAKIM
11/27/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 57674

MEETING MINUTES

Taiho Oncology, Inc.
Attention: Julie Boisvert
Senior Manager, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAS-102.

We also refer to the meeting between representatives of your firm and the FDA on July 31, 2014. The purpose of the meeting was to reach agreement on the content and format of your proposed NDA for TAS-102.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:

Final Meeting Minutes
CMC pre-NDA Meeting Minutes
Appendix I – OSI



MEETING COMMENTS

Meeting Type: Type B
Meeting Category: pre-NDA
Meeting Date and Time: July 31, 2014 from 11:30 AM – 1:00 PM
Meeting Location: CDER WO 22 – Room 1315
Application Number: IND 57674
Product Name: TAS-102; proposed proprietary name - Lonsurf[®]
Indication: Colorectal Cancer
Sponsor/Applicant Name: Taiho Oncology Inc.

FDA ATTENDEES

Office of Hematology and Oncology Products

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director, DOP 2
Steven Lemery, M.D., M.H.S., Team Lead, DOP 2
Abhilasha Nair, M.D., Medical Officer, DOP 2
Karen Jones, Chief, Project Management Staff, DOP 2
Ruth Maduro, Regulatory Project Manager, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2

Division of Hematology Oncology Toxicology, (DHOT)

Sachia Khasar, Ph.D., Toxicology Reviewer, DHOT

Office of Clinical Pharmacology

Division Clinical Pharmacology V, (DCP V)

Stacy Shord, Pharm.D, Clinical Pharmacology, Acting Team Lead DCP V
Jun Yang, Ph.D., Clinical Pharmacology Reviewer, DCP V

Office of Biostatistics

Division of Biostatistics V (DB V)

Xiaoping Jiang, Ph.D., Statistical Reviewer, DB V

Eastern Research Group Attendees

Patrick Liang

SPONSOR ATTENDEES

Manuel Aivado, M.D., Ph.D. Clinical Development and Pharmacovigilance, Taiho
Oncology, Inc. (TOI)
Hiroshi Ambe, B.Sc. Clinical Research, TOI

Gigi Atalla, R.Ph. Pharmacovigilance Operations, TOI
Fabio Benedetti, MD Chief Medical Officer, TOI
Eric Benn President and CEO, TOI
Lieselotte Bloss, DVM Regulatory Affairs, TOI
Julie Boisvert, B.Sc. Regulatory Affairs, TOI
Cliff Ding, Ph.D. Statistics, TOI
Hirokazu Mizuguchi, M.S. Clinical Research, TOI
Ken-ichiro Yoshida, Ph.D. Clinical Pharmacology, TOI

1.0 BACKGROUND

On May 15, 2014, Taiho Oncology Inc., (Taiho, formerly Taiho Pharma USA, Inc) requested a pre-NDA meeting to discuss and reach agreement on the content and format of the proposed NDA for the investigational product, TAS-102 (trifluridine/tipiracil hydrochloride). The meeting request granted letter was issued on 4 Jun 2014.

IND 57674 was submitted on 28 Dec 1998, in order to investigate TAS-102 as a treatment for patients with malignant solid tumors. Taiho submitted a request to inactivate IND 57674 on 15 Jun 2009; that request was granted and IND 57674 was inactivated on 23 Jun 2009.

On 24 Jun 2011, based on the results of a clinical trial conducted in Japan in patients with refractory colorectal cancer, Taiho reactivated IND 57674, and reinitiated clinical development of TAS-102 in the U.S. Taiho subsequently initiated a randomized, placebo-controlled, double-blind trial (TPU-TAS-102-301/ RECURSE) in USA, Europe, Japan, and Australia once the recommended dose was confirmed at 35 mg/m² in the western population. Prior to initiating the TPU-TAS-102-301 trial, a Type B EOP2 meeting was held on 12 Dec 2011 to discuss the trial design. During this meeting, FDA provided comments on issues related to the proposed dose in the US population, QT evaluation plan, clinical pharmacology evaluations, and the statistical analysis plan.

On 25 Oct 2013, the Office of Surveillance and Epidemiology granted Taiho's initial request for the proprietary name Lonsurf (pending resubmission of the request in an NDA).

Taiho stated that TAS-102 was approved in Japan on 24 Mar 2014, 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). Study J003 randomized 170 patients (2:1) with mCRC who progressed or failed to respond to at least two prior chemotherapy regimens that included a fluoropyrimidine, irinotecan, and oxaliplatin. Patients in the experimental arm received TAS-102 at a dose of 35 mg/m²/dose orally twice daily for five days a week (with two days rest) for 2 weeks, followed by a 14 day rest interval (repeated every four weeks). The primary endpoint of the trial was overall survival and the primary endpoint was tested with a one-sided alpha of 0.10. According to results that were described by Taiho and summarized in the 12 Dec 2011 meeting minutes, the study demonstrated that TAS-102 improved OS with a HR for OS of 0.56 with a p-

value of 0.0011 (median difference of 2.4 months). Although positive, the minutes noted baseline differences in prognostic factors between the treatment arms (e.g., 57% men in the treatment arm versus 49% for placebo).

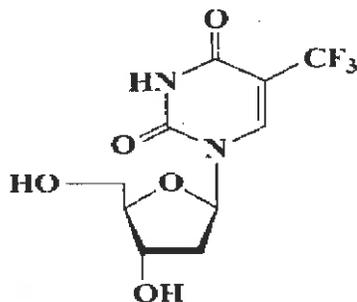
Chemical Name and Structure

TAS-102 (trifluridine/tipiracil hydrochloride), proposed proprietary name Lonsurf[®], is a fixed combination (1:0.5) of α,α,α -trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl- 2,4 (1H,3H)-pyrimidinedione hydrochloride [thymidine phosphorylase inhibitor (TPI)]. TAS-102 is supplied in two strengths: 15 mg white round tablets (containing 15mg FTD and 7.065 mg TPI as the active ingredients) and 20 mg pale-red round tablets (containing 20 mg FTD and 9.42 mg TPI as the active ingredients).

Structural Formula:

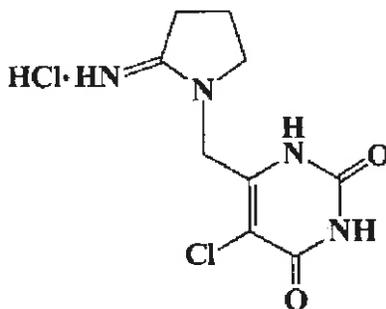
FTD :

α,α,α -trifluorothymidine or 2'-Deoxy-5-(trifluoromethyl)uridine



TPI :

2,4(1H,3H)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1)



Recommended Dose and Route of Administration

Taiho stated that the recommended starting dose in adults, for the immediate-release fill coated tablet, is 35 mg/m²/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).

The current global clinical development program of TAS-102 includes the following eight clinical studies as described in Table 1 below, for which final reports will be submitted as part of the planned NDA.

Study Design	Study Name	Function
Randomized, placebo controlled, double-blind	TPU-TAS-102-301 (RECOURSE)	"Pivotal study"
	J003-10040030 (Japan, phase 2)	
Open-label	J001-10040010 (dose-escalation, Japan, phase 1)	Supportive studies
	J004-10040040 (food effect, Japan, phase 1)	
	TPU-TAS-102-101 (dose escalation, U.S., phase 1)	
	TPU-TAS-102-102 (TPI PK contribution, U.S., phase 1)	
	TPU-TAS-102-103 (QTc, US/UK, phase 1)	
	TPU-TAS-102-104 (bioavailability, U.S., phase 1)	

Taiho stated that the clinical efficacy and safety of TAS-102 were evaluated in a multinational, double-blind, two-arm, parallel-group, randomized study in patients with refractory metastatic colorectal cancer (TPU-TAS-102-301; RECOURSE trial). Randomization in TPU-TAS-102-301 was stratified by KRAS status (wild type vs. mutant), Time since diagnosis of first metastasis (<18 months, ≥18months), and Region (Region 1: Asia [Japan]; Region 2: Western [US, Europe and Australia]). A total 800 eligible patients were randomly assigned in a 2:1 ratio to two treatment arms:

- Experimental: TAS-102 plus best supportive care (BSC) (n=534)
- Control: Placebo plus BSC (n=266)

Treatment was to continue until disease progression or unacceptable treatment-related toxicity.

TAS-102 or placebo was administered at a starting dose of 35 mg/m²/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). Treatment continued until disease progression or unacceptable toxicity.

Taiho stated that in the intent-to-treat (ITT) population, median age was 63 years, 61% of patients were men, 58% were White and 35% were Asian; all patients had a baseline ECOG performance status of 0 or 1.

The primary site of disease was colon for 62% of patients, and rectum for 38% of patients. *KRAS* mutation was present in tumor cells from 51% of patients. The majority of patients (61%) received ≥ 4 prior systemic cancer therapies. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; and all but 1 patient received bevacizumab. All but 2 patients with *KRAS* mutation-negative tumors had received panitumumab or cetuximab.

The primary endpoint was OS. The primary analysis was a stratified log-rank test performed on the ITT population. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of Jan 24, 2014 (4 patients died (b) (4)). The estimated median OS was 7.1 months for the TAS-102 group versus 5.3 months for the placebo group with a hazard ratio (HR) of 0.68 (95% confidence interval [CI]: 0.58, 0.81), $p < 0.0001$ (stratified log-rank test). The key secondary endpoint was progression-free survival (PFS) as assessed by the investigators. The estimated median PFS was 2.0 months for the TAS-102 group versus 1.7 months for the placebo group with a hazard ratio (HR) of 0.48 (95% CI: 0.41, 0.57), $p < 0.0001$ (stratified log-rank test).

Taiho stated that in the As Treated (AT) safety population [798 patients (533 in TAS-102 group and 265 patients in the placebo group)], the most frequently reported adverse events among patients who received TAS-102 were hematologic events, including neutropenia/neutrophil count decreased, anemia/hemoglobin decreased, and leukopenia/white blood cell count decreased; and gastrointestinal events, including nausea, diarrhea, and vomiting.

1. OBJECTIVE

- The purpose of this meeting is to obtain the Agency's guidance on the content and format of the TAS-102 NDA planned for December 2014.

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Preamble: In order to facilitate timely review of the NDA submission, Taiho should consider requesting Fast Track status in order to allow for submission of a rolling NDA. Specifically, FDA would recommend submitting, if ready (and complete) toxicology/non-clinical sections of the NDA prior to submission of other major components of the complete NDA. Please refer to 14 May 2014 FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.

Taiho Oncology's July 29, 2014 response to the Preamble: At your suggestion, we are currently considering several options relevant to fast track designation. One is to submit Module 4 and Module 2 sections 2.4 and 2.6 in September-October. Would this approach to submit partial Module 2 (complete sections 2.4 and 2.6) be acceptable?

We are currently also evaluating the possibility of submitting Module 3, Module 2 section 2.3 and relevant drug master files. What would be the latest acceptable date that would still provide value to the review team?

Discussion during the meeting: Taiho's proposal for submission of the nonclinical module in September-October 2014, if Fast Track designation is granted, is acceptable. FDA agreed that the proposal to submit a complete Module 3, Module 2, section 2.3, and referencing relevant drug master files may be acceptable, however, the contents of the complete sections will need to be discussed with the Office of New Drug Quality Assurance and the Office of Compliance and final agreement will be reached with submission of the schedule of a rolling application. The schedule should be included with the request for Fast Track designation.

Nonclinical

1. Does the Agency agree that the proposed non-clinical studies (pharmacology, safety pharmacology, pharmacokinetics and toxicology studies) would support the approval of TAS-102? (Content of Complete Application - Draft NDA Table of Content is presented in Attachment 3)

FDA Response: The table of nonclinical studies provided in attachment 4 of the meeting package appears sufficient to support the filing of an NDA. Until these studies are reviewed, FDA is unable to comment on the adequacy of the data to support the approval of a marketing application for TAS-102.

Taiho Oncology's July 29, 2014 response to question #1: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

2. The NDA will be prepared in the e-CTD format and submitted via ESG (Electronic Submission Gateway). All non-clinical information will be included in Module 4 except for information from 4 non-clinical studies using human material (Caco-2 cell permeability study, Study of Blood Cell Distribution of FTD and TPI, Plasma metabolite profiling and Search for TPI metabolites in human plasma and urine), which will be included in Section 5.3.2.3. Does the Agency concur with this approach?

FDA Response: No. Please include the information from the four non-clinical studies using human material (Caco-2 cell permeability study, Study of Blood Cell Distribution of FTD and TPI, Plasma metabolite profiling and Search for TPI metabolites in human plasma and urine) in Module 4 rather than Module 5.

Taiho Oncology's July 29, 2014 response to question # 2: We will include the non-clinical studies using human material in Module 4, as recommended. No further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

Clinical

3. The NDA clinical trial package will include the following: two well-designed, placebo-controlled randomized clinical trials (a single, global pivotal Phase 3 clinical trial in metastatic colorectal cancer patients (mCRC) and a supportive phase 2 trial in Japanese mCRC patients) and supportive data from six clinical pharmacology Phase 1 trials in different types of advanced cancer patients (See Attachment 5 for a brief description of the aforementioned trials).

Does the FDA agree that this clinical trial package is adequate for the registration of TAS-102?

FDA Response: Yes, the clinical trial package appears to be adequate to support the review of an NDA for the proposed indication; determination regarding approvability will be made once the application is submitted and reviewed. Note that the submission will be subject to a filing review to assess the adequacy and completeness of the application.

Taiho Oncology's July 29, 2014 response question #3: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

4. Since the demonstration of efficacy will be based on the single phase 3 pivotal trial, Taiho Oncology is not planning to perform a pooled efficacy analysis. Does the Agency concur with our proposal?

FDA Response: Yes, FDA agrees with the proposed plan not to submit a pooled efficacy analysis of Study J003-10040030 and study TPU-TAS-102-301 (RECOURSE) for the reasons included in the meeting package.

Taiho Oncology's July 29, 2014 response to question #4: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

5. Furthermore, the narrative portion of the ISE will be placed in Section 2.7.3 and will be referenced in Module 5, Section 5.3.5.3 (i.e., leaf elements will be provided in both locations). Does the FDA concur with our proposal?

FDA Response: Yes, FDA agrees that that it is reasonable to include the narrative portion of the ISE in Section 2.7.3 of the application with appendices of tables, figures, and datasets of the ISE located in Module 5, as described in FDA Guidance for Industry: Integrated Summaries of Effectiveness and Safety, April 2009. In the application, Taiho

will need to include a clear explanation of where parts of the application are located and provide working cross-links between the two modules. Note that the Summary of Clinical Efficacy is subject to space limitations, and FDA may refuse to file the application if the narrative summary in Section 2.7.3 is longer than 400 pages.

Taiho Oncology's July 29, 2014 response to question #5: Thank you, we will follow the recommendations listed above and FDA Guidance for Industry: *Integrated Summaries of Effectiveness and Safety*, April 2009. No further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

6. In the integrated summary of safety (ISS), Taiho Oncology plans to include 3 ISS data groups. Please refer to Section 6.2 for a brief outline of the presentation of safety information in the ISS. Does the FDA agree with our pooling plan and analysis data sets?

FDA Response: No. FDA recommends that safety data from the proposed ISS Data Group 1 should include safety data from any patient who received the TAS-102 starting dose of 35 mg/m² twice daily. Alternatively, Taiho can submit datasets that include a fourth safety group (maintain the current definition for Group 1) that includes all patients who received the TAS-102 starting dose of 35 mg/m² twice daily (Taiho would not need to generate new (or revised) study reports describing this safety group).

Taiho Oncology's July 29, 2014 response to question #6: Taiho would like to discuss FDA's recommendation to add patients to the ISS irrespective of their cancer type, as long as they received the starting dose of 35mg/m² twice daily. Therefore, we offer the summary below for your further consideration and to foster our discussion.

Using the data from the proposed clinical trial package (8 studies listed in Table 1 of the briefing document), the currently proposed ISS data group 1 comprises a total of 762 patients with mCRC who received the starting dose of 35mg/m² twice daily. Randomized, placebo-controlled trials represent an optimal way to delineate a drug's true safety profile and Taiho's safety data will include data from 2 randomized, placebo-controlled trials, which contribute a total of 646 TAS-102 treated patients (versus a total of 322 placebo-treated patients in those 2 randomized, placebo-controlled trials). Therefore, Taiho considers the proposed safety dataset to be sufficiently large and robust to enable the delineation of the safety profile of TAS-102. Adding patients with a starting dose of 35mg/m² twice daily to the integrated data group 1 irrespective of their underlying disease might introduce qualitative problems without adding quantitative advantages for the following reasons:

- the addition of patients with different cancers bears the risk of confounding the resulting safety profile with safety information that is primarily driven by the different cancer types; and

- the potential quantitative advantage of adding more patients with a starting dose of 35mg/m² twice daily irrespective of their underlying cancers is limited because in our proposed clinical trial package, there were only 68 additional patients who met this criterion. This would represent an additional 9% of patients, only;

Therefore, Taiho proposes to keep the ISS data groups in their current form, i.e. avoiding the integration of safety data for patients with different cancer indications into one single dataset.

Discussion during the meeting: In response to FDA's request for clarification, Taiho stated that there will be two datasets containing data from patients with colorectal cancer (CRC) in CDISC format, and a third dataset containing SAE information in patients with CRC or other diagnoses, which is not in CDISC. FDA agreed that this information would be sufficient to support review but requested that the third dataset include demographic information (e.g. age, gender, race and weight or body mass), dosing information, and the primary cancer diagnosis. Taiho will attempt to provide a flag in the datasets that identifies any patient who received the dose of 35 mg/m² twice daily.

7. Taiho Oncology is proposing a safety (SAEs) cutoff date of July 24, 2014 for the inclusion in the NDA that is planned for mid-December 2014. All SAEs reported for TAS-102 prior to the SAE cutoff, regardless of the TAS-102 dose or cancer type, will be reported in the NDA using the Pharmacovigilance database.

Does the Agency agree with our proposal?

FDA Response: Yes, FDA agrees with the proposed cutoff date of July 24, 2014, provided that the NDA is planned to be submitted mid-December 2014. FDA recommends a data cut-off for submission of safety data of no more than 6 months prior to the submission of the NDA.

Taiho Oncology's July 29, 2014 response to question #7: Thank you, no further discussion is necessary at the meeting

Discussion during the meeting: No discussion occurred.

8. At the time of submission, Taiho Oncology intends to request a priority review designation based mCRC being a serious condition for which TAS-102 provides significant improvements of safety or effectiveness of TAS-102 over placebo for the treatment of mCRC. If granted, we propose a 120-day safety-cutoff date of January 19, 2015 and submission date of March 19, 2015 for the 120-day safety update report. Furthermore, the proposed 120-day safety update report content is summarized in Section 6.2. Does the FDA agree with the proposed content and cut-off date?

FDA Response: FDA agrees with the proposed safety update cut-off date. However *if* the NDA receives priority review; however, FDA recommends submission of the safety update 90 days after submission of the NDA.

FDA does not agree with the proposed content. As stated in 21 CFR 314, an applicant shall update periodically its pending application with new safety information learned about the drug that may *reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling*. Therefore, FDA does not agree with the plan to submit all AEs reported from the RECURSE study between 31 Jan 2014 and the proposed safety update. Because a complete safety database (through the data cut-off date) is expected at the time of the initial NDA submission, additional safety data in the safety update should be minimal (limited to deaths and serious adverse events).

Note that FDA's determination regarding priority review is assigned to a NDA for a drug that treats serious conditions and which provide significant improvement in the safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition compared to available therapies (i.e., not on a significant improvement *over placebo*).

Taiho Oncology's July 29, 2014 response to question #8: Taiho agrees with FDA's recommendation and will not update the AE data from the RECURSE study in the 120-day safety update report. Taiho would like to discuss FDA's comment regarding priority review determination requirements. Taiho plans to request priority review for TAS-102 at the time of the NDA submission. The planned original NDA for TAS-102 will represent an application for a drug that treats a serious condition, and, if approved, would provide a significant improvement in safety and effectiveness.

Taiho considers metastatic colorectal cancer (mCRC) to meet the definition (and qualifying criteria) of a serious condition as stipulated in section III.A (section IV) of the FDA Guidance for Industry entitled "Expedited Programs for Serious Conditions – Drugs and Biologics" (May 2014). Furthermore, TAS-102 demonstrates the potential to be a significant improvement in effectiveness of the treatment of mCRC, as evidenced by the following:

The pivotal RECURSE study demonstrated a clinically meaningful and statistically significant improvement in OS for patients with mCRC (Hazard Ratio = 0.68). These patients had to have failed or had to be intolerant to ALL therapies approved at the time of the beginning of the RECURSE study, which started enrolment June 17, 2012. These therapies include a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and an EGFR antibody (if KRAS wild-type).

Of note, on September 27, 2012, FDA approved Stivarga for the same patient population that was studied in RECURSE. In a pre-specified analysis of the RECURSE data, Taiho examined the outcome of mCRC patients who received treatment with Stivarga prior to randomization to TAS-102 or placebo. Eighteen percent (18%, 144/800) of all randomized patients had received prior treatment with Stivarga (91 TAS-102 patients and 53 placebo patients had received prior treatment with Stivarga), all in the Western region due to availability of regulatory approvals. The same clinical benefit was observed irrespective of prior treatment with regorafenib, as evidenced by the OS Hazard Ratio of 0.69 for both comparisons.

In addition, though Stivarga does provide a treatment option for patients in the same refractory metastatic CRC setting as was evaluated in RECURSE for TAS-102, there still remains an urgent need for other effective treatment options. To note, a significant number of patients in the Phase III trial with regorafenib in refractory metastatic CRC were reported to have progressed in or within 2 months of treatment. For these patients, currently, there are no other effective treatment options.

Does the FDA agree that this rationale will support priority review?

Discussion during the meeting: FDA stated that Taiho's proposed approach for supporting a request for priority review designation appeared appropriate. Taiho agreed to submit the safety update at day 90 regardless of the review designation.

9. Taiho Oncology plans to include the individual case report forms and the Clinical Study Report (CSR) narratives for all patients who had a serious adverse event, who died within 30 days after the last dose of study medication, or who discontinued from study due to an adverse event. Does the Agency agree with our proposal?

FDA Response: FDA agrees with the plan regarding the submission of CRFs based on the criteria outlined above in the NDA; however, please be prepared to submit other CRFs promptly (e.g., within 1 week) upon request (including CRFs from legacy studies as was defined in the briefing package). Regarding patient narratives, please also provide patient narratives (from Study TPU-TAS-102-301) for those patients who prematurely terminated study drug for the following reasons: "other", lost to follow-up, physician decision, or subject decision.

Narratives summaries should contain the following components:

- subject age and gender
- signs and symptoms related to the adverse event being discussed
- an assessment of the relationship of exposure duration to the development of the adverse event
- pertinent medical history
- concomitant medications with start dates relative to the adverse event
- pertinent physical exam findings
- pertinent test results (for example: lab data, ECG data, biopsy data)
- discussion of the diagnosis as supported by available clinical data
- a list of the differential diagnoses, for events without a definitive diagnosis
- treatment provided
- re-challenge and de-challenge results (if performed)
- outcomes and follow-up information

- an informed discussion of the case, allowing a better understanding of what the subject experienced.

Taiho Oncology's July 29, 2014 response question #9: TPU-TAS-102-301 patient narratives from patients who prematurely terminated study drug for the following reasons: "other", lost to follow-up, physician decision, or subject decision will be added to the CSR. All patient narratives will include the information recommended above.

Discussion during the meeting: No discussion occurred.

10. Taiho Oncology will summarize the available information on the major elimination pathways as well as the metabolism of TAS-102 components in sections 2.4 (non-clinical overview) and 2.7.2 (clinical summary) of the NDA. In addition, Taiho Oncology is conducting a mass balance study (TPU-TAS-102-108) to confirm the available mass balance and metabolism information in humans. The CSR is anticipated to be issued in 2Q2015. Please refer to Attachment 2 for additional information. Does the agency agree with our approach and timelines?

FDA Response: Yes, FDA agrees. See additional clinical pharmacology comments.

Taiho Oncology's July 29, 2014 response question #10: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

11. Taiho Oncology is planning to initiate studies of TAS-102 in patients with hepatic impairment (TO-TAS-102-106) and renal impairment (TO-TAS-102-107) in 4Q 2014. The initial NDA will include a population PK analysis that will assess the impact of renal and hepatic impairment in our current studies. Does the Agency agree with our approach?

FDA Response: Yes, FDA agrees. See additional clinical pharmacology comments.

Taiho Oncology's July 29, 2014 response question #11: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

12. Taiho Oncology will provide the certification and disclosure statements only for investigators who participated in the pivotal Phase 3 study (TPU-TAS-102-301/RECOURSE). Does the Agency agree?

FDA Response: No, FDA does not agree with this proposal. Provide certification and disclosure statements for all investigators in any of the "covered clinical studies" that Taiho intends to submit to support the safety and efficacy of TAS-102 for the proposed indication. Specifically, FDA believes that J003-10040030 is a covered study as it provides data supporting the treatment effect claimed based on the TPU-TAS-102-

301 trial. For a detailed definition of what constitutes a covered clinical study please refer to 21CFR54.2(e) or the “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators”

<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf>.

Provide justification in the NDA for studies that Taiho believes is exempt from this requirement. FDA may refuse to file any marketing application supported by covered clinical studies that does not contain, for each clinical investigator who is not an employee of the sponsor, a certification that no financial interest or arrangement specified in 54.4(a)(3) exists, a disclosure statement identifying the specified financial interests or arrangements and the steps taken to minimize bias, or a certification that the applicant has acted with due diligence to obtain the required information but was unable to do so and stating the reason (21 CFR § 54.4(c)).

Taiho Oncology’s July 29, 2014 response question #12: Study J003-10040030 was not conducted under the IND. Retrospectively; we have contacted each site, and collected the financial disclosure (FD) of the principal investigator (PI). Of note, the organizational structure in Japan is such that the ultimate responsibility over safety and efficacy information resides with the PI, and accordingly all CRFs were in fact signed by the responsible PI. Therefore, FD was collected only from those responsible PIs and Taiho considers this to be in line with FDA “Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators”.

As suggested, we now consider that RECOURSE and J003-10040030 meet the “covered study” definition. Does the FDA have further comments?

Discussion during the meeting: FDA stated that Taiho’s approach is acceptable.

Electronic Submission

13. Supportive SAS programs (all analysis dataset programs, all table programs that include inferential statistics, and all figure programs that include survival or inferential statistics) will be provided for the following studies: TPU-TAS-102-101, TPU-TAS-102-102, TPUTAS-102-103, TPU-TAS-102-104, TPU-TAS-102-301, J001-10040010, J003-10040030 and J004-10040040, as well as the ISS. Additional SAS programs that will allow FDA to execute these programs will be provided for the Phase 3 study (TPU-TAS-102-301) and for the ISS. Does the Agency agree with our proposal?

FDA Response: The proposal is acceptable. However, the SAS programs that are provided in the NDA submission should be stand-alone programs, e.g. the programs can be used to reproduce the major efficacy and safety results in the Clinical Study Report and the proposed labeling. Also please provide a reviewer’s guide that provides descriptions of analyses, the names of datasets and variables used in those SAS programs.

Taiho Oncology's July 29, 2014 response to question #13: We will follow the recommendation listed above; no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

14. Based on the preliminary safety profile of TAS-102, we believe that the potential risks will be adequately addressed through labeling and that a REMS will not be necessary. Does the Agency concur with this approach?

FDA Response: Yes, on preliminary evaluation and based on the data provided in the meeting package, a REMS will not be required for filing. However, a formal determination on the need for a REMS will be determined during the review of the NDA.

Taiho Oncology's July 29, 2014 response to question #14: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

15. As proposed by Taiho Oncology (pre-NDA CMC Meeting Request dated 31 October 2013, Serial No. 0217) and accepted by the FDA (refer to Meeting Preliminary Comment letter dated 27 November 2013), Taiho Oncology will submit 12 months LTSS (long-term stability study) data for all three primary batches within 30 days from the original NDA submission. The original NDA will include 9 months long-term and 6 months accelerated stability data for three primary batches of drug product. Does that FDA have any additional comment?

FDA Response: FDA has no additional comments.

Taiho Oncology's July 29, 2014 response to question #15: Thank you, no further discussion is necessary at the meeting.

Discussion during the meeting: No discussion occurred.

Additional Comments

Clinical

16. FDA has the following preliminary comments regarding the proposed labeling in Attachment 6 of the briefing package. Lack of comment does not necessarily indicate FDA agreement with the Section. Prior to submitting a proposed label in the NDA, please ensure that the label conforms to the requirements set forth in the Physician Labeling Rule (see general comment below). To ensure timely review of the NDA, FDA strongly recommends following the labeling Guidance documents contained in the following web-link

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRul es/ucm084159.htm>.

Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments on those additional comments with the exceptions of the following:

- **Indications and Usage:** Do not use promotional terms (b) (4).
- **Recommended Dose:** The Dosage and Administration Section appears to be overly complicated and thus likely to result in medication errors. Provide justification that this level of complexity (e.g., multiple lengthy tables) is necessary to ensure safe use and that in the clinical trial experience these recommendations were followed consistently and accurately.

Taiho Oncology's July 29, 2014 response to additional comment #16 regarding the Recommended Dose under the "Dosage and Administration Section" of the proposed label: We would like to better understand the FDA's statement that the proposed recommended dose section is "overly complicated".

Discussion during the meeting: FDA requested that dosing information be provided in a clear, concise format; FDA suggested describing the recommended dose in text as an option rather than in the proposed (b) (4) format. Taiho will explore dosing strategies that are less complex than those used in the clinical trials and will propose these dosing strategies in the label if supported by clinical data.

- **Contraindication:** Refer to the Guidance document at the following weblink: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. Unless, you have data supporting the proposed (b) (4) contraindication, remove this contraindication from the label.
- **Warnings:** Based on the class of drugs, include a Warning notifying prescribers of the increased risk of severe toxicity in patients with known dihydropyrimidine dehydrogenase deficiency (DPD). Alternatively, provide data that the metabolism of trifluridine bypasses the DPD pathway.

Also, in order to support a Warning, provide data justifying (b) (4)

Taiho Oncology's July 29, 2014 response to additional comment #16 regarding the "Warnings and Precautions" Section of the proposed label: Taiho does not intend to provide a warning about DPD deficiencies because the primary enzyme involved in the catabolism of FTD is thymidine phosphorylase, and the primary enzyme involved in the activation of FTD is thymidine kinase 1. In contrast, DPD is not involved in the activation or in the catabolism of FTD. Therefore, DPD deficiency will not affect either the safety or efficacy of TAS-102.

Discussion during the meeting: In regards to the Warning regarding DPD deficiency, FDA acknowledged Taiho's response and agreed that a Warning does not appear necessary based on the response provided. Taiho agreed to provide the information supporting the metabolism of TAS-102 in the NDA to support the omission of a Warning based on DPD.

- **Overdosage:** Revise this Section based on human data if such data exists. This section should not include general information (b) (4)
 - **Mechanism of Action:** Remove all statements that imply comparative efficacy to other drugs (b) (4). This section should describe the mechanism of action and not make promotional claims.
17. As stated in the 12 Dec 2011 meeting minutes for the Type B meeting held between Taiho and FDA, Taiho will need to provide adequate justification that TPI is a necessary component of TAS-102 and why trifluridine alone (e.g., at a higher dose or more frequent schedule) is not sufficient to provide the proposed treatment effect. In addition to providing pharmacokinetic data to support this justification, FDA recommends that Taiho provide a discussion regarding the practicality (or lack thereof) if a patient were required to take trifluridine alone (without TPI).

Taiho Oncology's July 29, 2014 response to additional comment #17: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

18. FDA acknowledges that Taiho will submit datasets in CDISC format using Implementation Guide 3.1.2. Although FDA agrees that it is acceptable to use this version of CDISC for submission of datasets, FDA requests that Taiho include additional variables in the demographics dataset (i.e., variables included in more recent STDM versions) in order to facilitate timely review of the data. These variables include: actual treatment arm (i.e., actual treatment received), death flag, date of death, date of informed consent, and date of first exposure to study drug.

Taiho Oncology's July 29, 2014 response to additional comment #18: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

19. The briefing package contains the statement: "the analysis datasets will generally be modeled in accordance with the Analysis Data Model version 2.1: Implementation Guide version 1.0 but will deviate from these guidance documents where necessary to

accurately represent the data as it was collected and analyzed.” In the NDA, please describe deviations from the guidance documents to ensure timely review of the data.

Taiho Oncology’s July 29, 2014 response to additional comment #19: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

Clinical Pharmacology

Please address the following clinical pharmacology related questions in the NDA submission:

20. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

Taiho Oncology’s July 29, 2014 response to additional comment #20: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

21. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
22. What are the exposure-response relationships (dose-response, exposure-response) for safety?

Taiho Oncology’s July 29, 2014 response to additional comment # 21 & 22: For safety, Taiho will provide information about the exposure-response relationship in the NDA based on the results of J001-10040010 (n=21). In addition, we are preparing an exposure-response relationship analysis for efficacy and safety based on RECOURSE results, and this report is anticipated to be available in March 2015.

Discussion during the meeting: FDA stated that Taiho should submit all available population pharmacokinetic and exposure-response analyses at the time of the submission of the original NDA.

FDA stated that under the PDUFA V Program, FDA cannot agree to accept a major component, e.g., the exposure-response analyses for Study RECOURSE, as a late submission. Taiho will need to provide adequate justification as to why the original NDA submission is complete without these analyses. FDA further stated that if Taiho does not

plan to submit the exposure-response analyses for Study RECURSE with the original NDA, Taiho should propose a postmarketing requirement (PMR) or postmarketing commitment (PMC) to submit these analyses, including milestones, to the FDA for review within the original NDA submission.

23. How is the QT prolongation potential of TAS-102 assessed? What are the conclusions and proposed labeling description?

Taiho Oncology's July 29, 2014 response to additional comment #23: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

24. What are the characteristics of absorption, distribution, metabolism and excretion of TAS-102?

Taiho Oncology's July 29, 2014 response to additional comment #24: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

25. What are the effects of food on the bioavailability of TAS-102 and dosing recommendation with regard to meals or meal types?

Taiho Oncology's July 29, 2014 response to additional comment #25: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

26. What influence do the intrinsic factors (as listed below but not limited to) have on TAS-102 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?

- a. gender
- b. race
- c. weight
- d. disease
- e. genetic polymorphism
- f. hepatic impairment
- g. renal impairment

Taiho Oncology's July 29, 2014 response to additional comment #26: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments.

Discussion during the meeting: No discussion occurred.

27. What influence do the extrinsic factors (as listed below but not limited to) have on TAS-102 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

Taiho Oncology's July 29, 2014 response to additional comment #27: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments.

Discussion during the meeting: No discussion occurred.

In addition, please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

28. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Taiho Oncology's July 29, 2014 response to additional comment #28: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments.

Discussion during the meeting: No discussion occurred.

29. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The subject's ID number in PK datasets should be consistent to those in datasets submitted for clinical review.

Taiho Oncology's July 29, 2014 response to additional comment #29: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments.

Discussion during the meeting: No discussion occurred.

30. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Taiho Oncology's July 29, 2014 response to additional comment #30: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

31. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

Taiho Oncology's July 29, 2014 response to additional comment #31: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

32. Provide a table listing of patients with renal or hepatic impairment who have received TAS-102, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Taiho Oncology's July 29, 2014 response to additional comment # 32: We will prepare a table as requested above. Could the FDA suggest the preferred location of this table in the eCTD? Would FDA be willing to review a mock output after the meeting for comments? If feasible, could the FDA please indicate to whom this table should be submitted for review?

Discussion during the meeting: FDA stated that the table, and its associated transport and programming files, should be submitted in Module 5: Clinical Study Reports under Section 5.3.5.3 Reports of analyses of data from more than one study. FDA stated that a mock output report would not be reviewed and therefore, Taiho should not submit the report.

33. Submit the following datasets to support the population PK analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - Description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)
- Model development decision tree and/or table which gives an overview of modeling steps

For the population analysis reports, submit

- Standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information

Taiho Oncology's July 29, 2014 response to additional comment #33: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

34. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for TAS-102 and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

Taiho Oncology's July 29, 2014 response to additional comment #34: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

35. Submit the following items for QTc study/assessment
- Copy of the QT/QTc study protocol
 - Copy of the Investigator's Brochure
 - Annotated CRF
 - Define file which describes the contents of the electronic data sets
 - Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - Completed Highlights of Clinical Pharmacology Table

Taiho Oncology's July 29, 2014 response to additional comment #35: Taiho would like to thank the FDA for providing additional comments to help us prepare the TAS-102 NDA. We have no further comments

Discussion during the meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- FDA and Taiho reached general agreement on the contents and format of the all modules of the NDA.
- FDA and Taiho reached agreement on the content of a complete application. FDA agreed that the following minor component may be submitted no later than 30 calendar days:
 - 12 months stability data for all three primary batches.
- The application will include comprehensive and readily available lists of all clinical and manufacturing sites. Taiho stated that the OSI datasets limited to the RECURSE Study will be submitted to the IND or NDA prior to submission of the last module of the NDA (i.e., the complete application).
- Based on the preliminary safety profile of TAS-102 provided by Taiho in the meeting package, a REMS will not be required for filing, however, a formal determination on the need for a REMS will be determined during the review of the NDA.
- FDA recommended that Taiho submit a request for Fast Track designation that includes the schedule for a rolling NDA submission.
- On November 27, 2013 the Office of New Drug Quality Assessment issued preliminary comments to Taiho Oncology, Inc., (formerly known as Taiho Pharma USA, Inc.) in response to the questions contained in the October 31, 2013 briefing document in preparation for the December 5, 2013 face to face meeting with Taiho Oncology.

Taiho Oncology reviewed the preliminary comments and elected to cancel the December 5, 2013 face to face meeting as no further explanation or clarification of the preliminary responses was required.

The preliminary comments issued on November 27, 2013 stand as the final pre-NDA CMC meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities responsible for the commercial process, associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

In addition to commercial manufacturing facilities, please include all manufacturing facilities where batches were made to support the application (if they differ from facilities intended for commercial manufacturing). Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

THE OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

Appendix I contains information that will facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments. The Agency strongly encourages Taiho Oncology to formally submit the information noted in Appendix I (Item I and Item II) to the IND prior to submission of the NDA.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 57674

MEETING MINUTES

Taiho Pharma USA, Inc.
Attention: Julie Boisvert
Global Senior Director, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Ms. Boisvert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAS-102.

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2011. The purpose of the meeting was to obtain guidance from the Agency on the proposal of the Phase 3 clinical trial of TAS-102 in refractory colorectal cancer patients and the ancillary studies required in support of your clinical development and registration plans of TAS-102.

Copies of the official minutes, your slide presentation and the attendance log are enclosed. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Meeting Minutes
Taiho Slide Presentation
Attendance Log

MEMORANDUM OF MEETING MINUTES

SPONSOR: Taiho Pharma, U.S.A., Inc.
MEETING DATE: December 12, 2011
TIME: 3:00 PM – 4:00 PM
LOCATION: CDER WO Building 22, Room 1415
APPLICATION: IND 57674
DRUG NAME: TAS-102
TYPE OF MEETING: Type B, End of Phase 2
MEETING CHAIR: Steven Lemery
MEETING RECORDER: Gina Davis

FDA ATTENDEES:

Patricia Keegan	Director, Division of Oncology Products 2
Joseph Gootenberg	Deputy Director, Division of Oncology Products 2
Steven Lemery	Team Lead, Division of Oncology Products 2
Robert White	Medical Officer, Division of Oncology Products 2
Richard Pazdur	Director, Office of Hematology and Oncology Products
Gregory Reaman	Associate Director, Oncology Sciences, Office of Hematology and Oncology Products
Hong Zhao	Team Lead, Division of Clinical Pharmacology V
Ruby Leong	Reviewer, Division of Clinical Pharmacology V
Kun He	Biostatistics Team Lead, Office of Biostatistics V
Jenny Zhang	Biostatistics Reviewer, Office of Biostatistics V
Gina Davis	RPM, Division of Oncology Products 2

TAIHO PHARMA, U.S.A., Inc. ATTENDEES:

Eric Benn	President
Fabio Benedetti	Chief Medical Officer
Hiroshi Ambe	Clinical Research
Daljit K. Gill	Regulatory Affairs
Julie Boisvert	Regulatory Affairs
Donghu Lin	Clinical Development
Junichi Saruta	Global Business Development and Commercialization
Shigeru Takagi	Clinical Development and Pharmacovigilance
Kazumasa Ikeda	Pharmacokinetics
Masanobu Ito	Management of Clinical
Ken-ichiro Yoshida	Pharmacokinetics
Hiroyuki Okabe	Pharmacology
Robert J. Mayer (call-in)	Principal Investigator Phase 3 clinical trial
Lloyd Whitfield	Pharmacokinetics
Lukas Makris	Statistics

1.0 BACKGROUND:

On September 8, 2011, Taiho Pharma U.S.A., Inc. (Taiho) requested a Type B End of Phase 2 meeting with the Division of Drug Oncology Products, now the Division of Oncology Products 1. On September 12, 2011, the meeting request was transferred to the Division of Oncology Products 2 (DOP 2) due to the reorganization of the Office of Hematology and Oncology Products.

Taiho requested this meeting to discuss TPU-TAS-102-301, a randomized clinical trial intended to support the registration of TAS-102 for the treatment of patients with refractory colorectal cancer.

TAS-102 is a fixed combination (1:0.5) of α,α,α -trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl- 2,4 (1H,3H)-pyrimidinedione hydrochloride [thymidine phosphorylase inhibitor (TPI)]. TAS-102 is supplied in two strengths: 15 mg white round tablets (containing 15mg FTD and 7.065 mg TPI as the active ingredients) and 20 mg pale-red round tablets (containing 20 mg FTD and 9.42 mg TPI as the active ingredients). In the meeting package, Taiho stated that the mechanism of action of FTD is through the inhibition of thymidylate synthase (TS) and that the investigational drug is an antimetabolite. Taiho also stated that FTD differs from 5-FU in that FTD is incorporated into DNA to a larger degree. Taiho stated that TPI prevents the rapid degradation of FTD allowing twice daily oral administration of FTD and that plasma FTD reached a maximum level at the molar ratio of 1:0.5 FTD to TPI.

IND 57674 was submitted on December 28, 1998, and inactivated on June 23, 2009. Based on the results of an exploratory randomized trial, in Japan, in patients with refractory colorectal cancer, Taiho reactivated IND 57674 on June 24, 2011, and reinitiated clinical development of TAS-102 in the U.S.

A separate teleconference was held on November 29, 2011 between Taiho, the Office of New Drug Quality Assessment and the Division of Hematology and Oncology Toxicology.

To date, six dose-finding TAS-102 monotherapy trials have been completed (see table below), each with a different dosing schedule. Taiho also conducted two activity estimating trials in patients with gastric and colorectal cancer.

In five of the TAS-102 dose-finding trials conducted in the US, a total of 111 patients were enrolled and treated. All 111 patients experienced adverse events (AEs). Two patient deaths were reported during the five studies. One patient died during Study TAS-102-9803, and one patient died during Study TAS-102-9805; both deaths were considered by the Investigator to be not related to study drug. Twenty-two (22) serious adverse events (SAEs) were reported by 19 patients. Two SAEs were considered by the Investigator to be related to study drug: an SAE of colitis and an SAE of deep venous thrombosis reported in 1 patient each.

A summary of the 6 Phase 1 TAS-102 monotherapy trials.

Trial	Regimen/Dosage	N	Malignancy (% of Patients)^a	Prior Therapies (median)	MTD (mg/m²/day)	DLT
US Trial TAS102-9801	2 weeks with 1 week rest, repeated every 3 weeks / QD	14	CRC (100%)	4	50	Granulocytopenia
US Trial TAS102-9802	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / QD	24	CRC (83.3%)	3.5	100	Granulocytopenia
US Trial TAS102-9803	5 days every 3 weeks / QD	39	CRC (82.1%)	4	160	Granulocytopenia and others
US Trial TAS102-9804	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / BID	19	BC (100%)	5	50	Granulocytopenia and others
US Trial TAS102-9805	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / TID	15	CRC (60%)	3	70	Granulocytopenia and others
Japan Trial J001/10040010	5 days with 2 days rest for 2 weeks, repeated every 4 weeks / BID	21	CRC (85.7%)	3	70	Granulocytopenia and others

^a CRC=Colorectal cancer; BC=Breast cancer

One activity estimating trial in gastric cancer (2nd line) was conducted in the US (Study TAS102-9806). This trial was an open-label, Simon 2-stage, single-arm study evaluating TAS-102, 50 mg/m² per day administered orally (25 mg/m²/dose twice daily) for 5 consecutive days with 2 days rest weekly for 2 weeks followed by a 2-week recovery period. The regimen was repeated every 4 weeks until disease progression. Taiho enrolled a total of 18 patients and reported a 0% overall response rate, prompting Taiho to close the study after the first stage.

Taiho conducted a randomized activity estimating trial in patients with colorectal cancer in Japan (Study J003/10040030). The primary efficacy and safety analyses of this study have been completed and as of 03 October 2011, no patients remain on treatment. The trial was a randomized (2:1), double-blind, placebo-controlled study of patients with chemotherapy-refractory advanced colorectal cancer who progressed or failed to respond to more than two chemotherapeutic regimens including a fluoropyrimidine, irinotecan, and oxaliplatin. TAS-102 plus best supportive care (BSC) was administered at a dose of 70 mg/m²/day (35 mg/m²/dose twice daily) for 5 consecutive days with 2 days rest weekly for 2 weeks followed by a 2-week recovery period. Patients in the placebo arm received BSC. The primary endpoint was overall survival (OS) and designed with a one-sided alpha of 0.10. Taiho enrolled 172 patients; however the full analysis set consisted of 169 patients. Two patients were excluded by Taiho and discontinued prior to receiving study drug. In the submission, Taiho reported a HR for OS of 0.56 with a p-value of 0.0011 for OS (median difference of 2.4 months). PFS was also reported to be improved; however, ORR was similar between arms (0.9% in the treatment arm versus 0% in the control arm). Some baseline differences in prognostic factors were observed in the trial between arms (57% of patients were men in treatment arm versus 49% in placebo arm; 44% of patients had rectal cancer in the treatment arm versus 37% in the placebo arm).

The randomized trial allowed for a comparison of safety between arms. One patient in the treatment arm experienced fatal pneumonitis. The following table describes severe (\geq Grade 3) events that occurred more frequently in the treatment arm in Trial J003/10040030 (at least 2% in the TAS-102 arm and \geq 2% higher in the TAS-102 arm compared to placebo). SAEs of febrile neutropenia occurred in 4.4% of patients receiving TAS-102 and 2.7% of patients receiving TAS-102 experienced an SAE of pneumonia.

<u>Event</u>	<u>TAS-102 (%)</u>		<u>Placebo (%)</u>	
	<u>N=113</u>		<u>N=57</u>	
	<u>Grade 3</u>	<u>Grade 4</u>	<u>Grade 3</u>	<u>Grade 4</u>
<u>Diarrhea</u>	<u>6.2</u>	<u>0</u>	<u>0</u>	<u>0</u>
<u>Vomiting</u>	<u>3.5</u>	<u>0</u>	<u>0</u>	<u>0</u>
<u>Fatigue</u>	<u>6.2</u>	<u>0</u>	<u>0</u>	<u>3.5</u>
<u>Hemoglobin decreased</u>	<u>10.6</u>	<u>6.2</u>	<u>3.5</u>	<u>1.8</u>
<u>Lymphocytes decreased</u>	<u>8</u>	<u>1.8</u>	<u>3.5</u>	<u>0</u>
<u>Neutrophils decreased</u>	<u>31.9</u>	<u>18.6</u>	<u>0</u>	<u>0</u>
<u>Platelets decreased</u>	<u>3.5</u>	<u>0.9</u>	<u>0</u>	<u>0</u>
<u>WBC decreased</u>	<u>25.7</u>	<u>2.7</u>	<u>0</u>	<u>0</u>

Proposed Phase 3 Trial

Taiho proposes a multinational, double-blind, two-arm, parallel, randomized comparison study to evaluate the efficacy and safety of TAS-102 versus placebo in patients with colorectal cancer who have received two or more prior standard therapies for metastatic colorectal cancer. Standard therapies must include all of the following drugs approved in each country (fluoropyrimidines, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody, and an anti-EGFR antibody for patients with wild-type KRAS). Patients will be randomly assigned (2:1) to TAS-102 (experimental arm) or placebo (control arm). Randomization will be stratified by KRAS status (wild, mutant), time since diagnosis of metastases (< 18 months versus \geq 18 months), and geographical region [Region 1: Asia (Japan); Region 2: Western (U.S. and Europe)].

Patients randomized to the experimental arm will receive 35 mg/m² TAS-102, twice daily for five days followed by two days of rest for two weeks (doses administered on days 1 through 5 and 8 through 12) followed by a 14 day recovery period.

The primary endpoint is overall survival (OS), and the study design has 90% power to detect an improvement in median OS of 1.7 months (hazard ratio of 0.75) at a one-sided alpha of 0.025. The assumed median survival duration in the control arm is 5 months. A total of 800 patients will be enrolled into the study with a target of 571 deaths for the primary analysis. The primary analysis will be a stratified log-rank test performed on the ITT population using IVRS stratification. No interim analyses for efficacy or futility are planned. Secondary end-points include progression-free survival and safety and tolerability.

Taiho states that all patients will be followed for survival at scheduled 8-week time intervals until death. Patients will be followed up to 1 year after the last patient has been randomized in the study. If a patient is still receiving study medication at the end of this period, continuation of TAS-102 and follow-up procedures will be decided on a case-by-case basis.

2.0 MEETING OBJECTIVES:

- To obtain the Agency's guidance on the proposed pivotal Phase 3 clinical trial of TAS-102 in refractory colorectal cancer patients and on the ancillary studies required to support the clinical development and registration of TAS-102.

Sponsor Submitted Questions and FDA Responses

1. Is the proposed pivotal Phase 3 clinical trial, as designed, together with the randomized, double-blind, placebo-controlled Phase 2 clinical trial conducted in Japan (TAS102-J003), adequate to support the registration of TAS-102 for the treatment of refractory colorectal cancer, as it is defined in the protocol?

FDA Response: No. Although TAS-102-301 may be adequate in design to provide data to support registration, Taiho has not established that the proposed dosing regimen for TAS-102-301 is reasonably safe for the U.S. population (U.S. Trial TAS-102-9804

established 25 mg/m² twice daily as the MTD). FDA expects that Taiho will complete the ongoing sequential, dose-escalation safety and tolerability trial, TAS-102-101, conducted in the U.S., in order to establish that the proposed dose in trial TAS-102-103 is reasonably safe.

To support an NDA, Taiho will need to justify that the results are applicable to the U.S. population. FDA expects that Taiho will enroll adequate numbers of patients in the TAS-201-301 trial who received prior therapy applicable to a U.S. population and who reflect an ethnic composition sufficiently similar to that of the U.S. population.

Also, for a single randomized trial to support an NDA powered at a one-sided alpha of 0.025, the trial should be well designed, well-conducted, and internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Acceptance of the results of a single trial will be based upon magnitude of effect and robustness of results and will be a review issue. Please refer to FDA guidance documents “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf> and “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to question # 1: Taiho will not start the TAS-102-301 trial in the U.S. until at least 18 evaluable patients in TAS-102-101 have completed Cycle 1 and the sponsor has established that the proposed dose regimen is reasonably safe. Does the FDA concur with this proposal?

We acknowledge your other comments pertaining to the TAS-102-301 trial.

Discussion during the meeting: FDA stated that the proposed approach to evaluate safety in 18 patients at the MTD after cycle 1 appears reasonable; however, acceptance of the proposed dose regimen will be a review issue at the time that the protocol is submitted to the IND.

2. Is the proposed clinical study to evaluate the pharmacokinetics of FTD with and without TPI, together with the evaluation of safety and efficacy of the TAS-102 combination in the proposed pivotal Phase 3 clinical trial, adequate to meet the contribution of parts criteria for TAS-102?

FDA Response: In an NDA submission, Taiho will need to provide adequate justification 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. Please refer to the draft Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf>.

However, the general study design for the proposed pharmacokinetics study appears to be acceptable to characterize the pharmacokinetics of FTD with and without TPI. Submit the protocol for FDA review and detailed comments will be provided at the time of protocol review.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 2: Taiho thanks FDA for the comment. Taiho will submit the protocol for review.

Discussion during the meeting: No discussion occurred regarding question 2.

3. Are the proposed renal and hepatic impairment study designs adequate to support TAS-102 marketing registration?

FDA Response: The general study design for the proposed renal and hepatic impairment trials appear to be acceptable. The trials should be conducted as per Guidance for Industry, "Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> and Guidance for Industry, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>. The adequacy of the trials to support TAS-102 registration will be a review issue. Please submit the protocols for FDA review and detailed comments will be provided at the time of protocol review. Please provide adequate justification/ rationale to support administration of TAS-102 under fed conditions in both proposed studies. See comment #7.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 3: Taiho thanks FDA for the comment. Taiho will submit the protocols for review.

Justification to support performing the studies under fed conditions is provided in response to Comment #7.

Discussion during the meeting: No discussion occurred regarding question 3.

4. Is the proposed plan to evaluate QT/QTc prolongation adequate to support TAS-102 marketing registration?

FDA Response: The overall QT risk evaluation plan is inadequate to support TAS-102 marketing registration. FDA generally recommends conducting a thorough QT trial for TAS-102. However in oncology, alternative proposals to the thorough QT trial may be

appropriate. Until a dedicated QT clinical trial is conducted to rule out the risk of TAS-102 causing QT prolongation, conduct ECG monitoring in all clinical trials (including all patients in the renal and hepatic impairment studies) at baseline, around the anticipated maximal plasma concentration after first dose, at steady-state concentration, at the end of treatment, and as clinically indicated. For more information, refer to the Guidance for Industry entitled, "E14 Clinical Evaluation of QT/QTc Interval Prolongation" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>. Please submit your QT assessment protocol for FDA review.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 4: Taiho acknowledges FDA's comment. No further discussion needed.

Discussion during the meeting: No discussion occurred regarding question 4.

ADDITIONAL COMMENTS

Clinical

5. In the proposed protocol, TAS-102-301, submitted to the IND
- a. Specify that the final analysis will occur when the target number of events is reached (rather than potentially allowing an analysis one year after the last patient is randomized as described on pages 30 to 31 of the protocol).

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(a): Taiho agrees and will amend the protocol appropriately.

Discussion during the meeting: No discussion occurred regarding additional comment 5(a).

- b. Revise the Sample Size section (5.4.3.1) to specify how the median survival time of the control arm was estimated (i.e., from Japan, US, or other).

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(b): Taiho agrees and will amend the protocol appropriately.

Discussion during the meeting: No discussion occurred regarding additional comment 5(b).

- c. Include a testing procedure to adjust for multiplicity for testing secondary endpoints [e.g., a sequential testing procedure for the following endpoints: (1) OS, (2) PFS and (3) ORR] in the ITT population.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(c): Please see also statement in section 10.3.2.3 "All secondary endpoints comparisons will be made at the 2-sided 0.05 significance level. Since PFS is the only key secondary endpoint for regulatory registration purposes, no further multiplicity adjustments will be made."

The only secondary endpoint for labeling consideration is PFS, identified as the key secondary endpoint. As such, assuming that the primary endpoint demonstrates significance at the 1-sided 0.025 level, PFS will subsequently be tested at the 1-sided 0.025 level. Additional clarification will be added about the sequential testing procedure, assuming that the primary endpoint yields significant results.

Does the FDA concur with this proposal?

Discussion during the meeting: FDA agreed that the proposal is acceptable.

- d. Provide evidence that TAS-102 can be safely administered (as described in Section 6.1.3.3 of the protocol) at the same dose in the presence of uncomplicated neutropenia or thrombocytopenia (irrespective of the nadir neutrophil or platelet counts observed).

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(d): Taiho requests that the FDA clarifies their concerns and we would like to discuss this comment further.

Discussion during the meeting: Taiho agreed to clarify in the protocol that uncomplicated grade 4 neutropenia or thrombocytopenia leading to more than a one week delay in initiation of the next cycle would result in subsequent doses being reduced per the reduction criteria in the protocol. FDA agreed that if the next cycle was delayed by one week or less no dose reduction would be required.

- e. Provide justification for allowing continued dosing of TAS-102 following the occurrence of more than one Grade 4 non-hematological adverse event.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(e): Taiho requests that the FDA clarifies their concerns and we would like to discuss this comment further.

Discussion during the meeting: Taiho acknowledged FDA's comment and will address this issue in the final version of the protocol.

- f. Clearly define symptomatic deterioration (due to colon cancer) in the absence of progression that will result in a patient discontinuing study therapy. Please ensure

that discontinuation due to “symptomatic deterioration” is clearly differentiated from objective radiographic progression on the CRFs. Removal of an excess number of patients from therapy due to “symptomatic deterioration” may limit the ability to make labeling claims based on the secondary endpoint of PFS.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to question # 5(f): Taiho will attempt to further define symptomatic deterioration in the absence of progression in the protocol; however, we are not aware of any standard definition for this.

Does the FDA have recommendations or guidance?

Taiho confirms that the CRF will capture the differentiation between discontinuation due to symptomatic deterioration and objective radiographic progression.

Discussion during the meeting: FDA had no specific recommendation or guidance. FDA and Taiho agreed that the protocol can remain in the present form on this issue.

- g. Revise page 58 (third paragraph) so that CTCAE is used to grade the severity of adverse events (rather than for “reporting” adverse events). Please ensure that verbatim adverse event terms are captured in the CRFs in order to permit a substantive analysis of adverse events using MedDRA.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to question # 5(g): Taiho agrees and will amend the protocol appropriately.

Discussion during the meeting: No discussion occurred regarding additional comment 5(g).

- h. Revise the definition of causal relationship for AEs on page 58 to require a clear alternative explanation regarding why an AE is considered not related to TAS-102 (rather than “could have been produced by a documented pre-existing condition, concomitant medication, or patient’s clinical state).

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to question # 5(h): Taiho agrees and will amend the protocol appropriately.

Discussion during the meeting: No discussion occurred regarding additional comment 5(h).

- i. Correctly identify EGFR as *epidermal* growth factor receptor (FDA noted probable errors on page 13 of 181 of the meeting package and in the protocol on

pages 3 and 17) or clarify in the protocol if Taiho is actually referring to a separate *endothelial* growth factor receptor.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(i): Thank you. The protocol will be corrected.

Discussion during the meeting: No discussion occurred regarding additional comment 5(i).

6. FDA suggests that Taiho consider conducting an additional randomized dose finding study in North America and Western Europe in order to ensure optimal design of the TAS-102-301 trial. Such a trial can assist Taiho in determining the optimal dose, in refining effect size assumptions based on different regions, and in further exploring whether the potential interaction based on KRAS status is a true effect or occurred due to the small sample size of trial J003/10040030.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to question # 5(i): Taiho acknowledges additional comment 6.

Discussion during the meeting: No discussion occurred regarding additional comment 6.

Clinical Pharmacology

7. Provide justification and data to support the administration of TAS-102 under fed conditions in the ongoing and proposed clinical trials.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to additional comment 7: After oral administration of [14C-FTD]TAS-102 (50 mg/kg) to non-fasting male rats, C_{max} and AUC_{0-∞} of FTD were comparable with those in the fasting male rats. After oral administration of [14C-TPI]TAS-102 (50 mg/kg) to non-fasting male rats, C_{max} of TPI was lower while AUC_{0-∞} was comparable with those in the fasting male rats. Based on the animal data, the exposure to FTD in human after administration of TAS-102 was expected to not be affected by food.

In earlier clinical studies, TAS102-9801, 9802 and 9803, TAS-102 was administered in once daily schedule before meals. In clinical studies, TAS102-9804 and later, multiple time daily dosing was investigated, and TAS-102 was administered after meals. This change was made with the expectation for better medication compliance.

The recommended dosage in the ongoing and proposed clinical trials was determined in Japanese phase 1 study, where TAS-102 was administered twice daily for 5 days a week followed by 2 days rest for 2 weeks after meals. This dosing regimen was then used in

study TAS102-J003, the results of which provide the rationale for the current development program.

Discussion during the meeting: A food effect study is ongoing and will be completed prior to the start of other proposed clinical trials. The results will be used to determine the dosage strategy for the Phase 3 trial with regard to food. Taiho agreed to submit the data to the FDA prior to initiation of additional clinical studies.

8. Conduct a food effect study as per Guidance for Industry, “Food –Effect Bioavailability and Fed Bioequivalence Studies” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf> before initiating other proposed clinical trials, including the Phase 3 trial and clinical pharmacology studies. Results of the food effect study will guide the decisions to administer TAS-102 with or without food in these proposed trials.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 8: A food effect study is ongoing and will be completed prior to the start of other proposed clinical trials.

Discussion during the meeting: No discussion occurred regarding additional comment 8.

9. Conduct population pharmacokinetic analysis to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of TAS-102 in humans. Refer to the Guidance for Industry “Population Pharmacokinetics” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 9: Taiho acknowledges additional comment 9.

Discussion during the meeting: No discussion occurred regarding additional comment 9.

10. Collect sparse PK samples in the proposed Phase 3 trial to explore the exposure-response relationships for FTD and TPI (and metabolites) for measures of both effectiveness and toxicity. Refer to the Guidance for Industry, “Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 10: Taiho acknowledges additional comment 10.

Discussion during the meeting: No discussion occurred regarding additional comment 10.

11. Validate the analytical methods used to determine the concentrations of FTD and TPI (and metabolites). Refer to the Guidance for Industry “Bioanalytical Method Validation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 11: Taiho acknowledges additional comment 11.

Discussion during the meeting: No discussion occurred regarding additional comment 11.

12. Evaluate the *in vitro* ability of FTD and TPI (and metabolites) to act as substrates, inhibitors or inducers of cytochrome P450 enzymes, and/or of transporters to determine the need for pharmacokinetic drug interaction trial(s). Refer to the Guidance for Industry “Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 12: Taiho acknowledges additional comment 12.

Discussion during the meeting: No discussion occurred regarding additional comment 12.

13. Identify the pathways by which FTD and TPI (and metabolites) are eliminated.

Taiho Pharma’s December 9, 2011, electronic (email) response to FDA’s December 7, 2011 preliminary response to additional comment 13: Taiho acknowledges additional comment 13.

Discussion during the meeting: No discussion occurred regarding additional comment 13.

14. Conduct the same clinical pharmacology studies for each of the individual drugs in the development of the combination as would be done if the drugs were being developed separately. In general, such studies include the assessment of bioavailability, characterization of pharmacokinetics, mass balance, the evaluation of effects of intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors on pharmacokinetics and pharmacodynamics, and exploring

exposure-response relationships. Studies to address intrinsic and extrinsic factors could be conducted with the combination instead of the individual drugs. Refer to the draft Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf>.

Taiho Pharma's December 9, 2011, electronic (email) response to FDA's December 7, 2011 preliminary response to additional comment 14: Taiho would like to discuss this comment further.

Discussion during the meeting: FDA stated that Taiho will need to provide justification regarding not conducting BA studies for individual components. Taiho agreed to submit justification to the IND. Taiho requested a separate teleconference to discuss FDA's recommendation for mass balance study. FDA stated that documentation can be submitted to the IND, and FDA will contact Taiho if additional data are needed.

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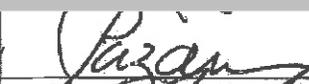
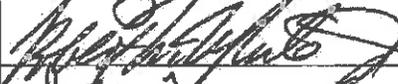
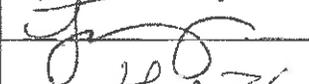
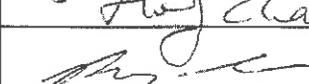
MEETING ATTENDEES

Date: December 12, 2011

Time: 3:00 PM – 4:00 PM

Place: CDER WO 22, Rm 1415

Firm: Taiho Pharma, U.S.A., Incorporated

NAME	SIGNATURE	TITLE	REPRESENTING
DANIEL GIL	(b) (4)	Regulatory Affairs	Taiho
Faiz BENN	(b) (4)	PRESIDENT + CEO	TAIHO
Shigoru TAKAGI	(b) (4)	Clinical Res.	TAIHO
Junichi SAKURA	(b) (4)	Global Business	TAIHO
Kazumasa Ikeda	(b) (4)	Pharmacofhetics	TAIHO
Hiroyuki Okabe	(b) (4)	Pharmacology	TAIHO
Dong hu Lin	(b) (4)	Clinical Development	TAIHO
Lukas Marri	(b) (4)	Statistics	TAIHO
FABIO BENEDETTI	(b) (4)	CHIEF MEDICAL OFFICER	TAIHO
Wlad Whitford	(b) (4)	Clinical Pharmacology	TAIHO
Ken-ichiro Yoshida	(b) (4)	Pharmacokinetics	Taiho Japan
Hiroshi Ambe	(b) (4)	Clinical Research	Taiho
MASANOBU ITO	(b) (4)	Management of Clinical	Taiho
JULIE BOISVERT	(b) (4)	Regulatory Affairs	Taiho
RICHARD PARDUN			FDA
Robert White		Oral drug - new	FDA
Steven Lemery		team leader	FDA-DoP2
Jenny Zhang		ORAL statistician	FDA
Hong Zhao		TL Clin Pharm	DCP5/ocp/ots
Ruby Leung		Clin Pharm Reviewer	DCP5/ocp/ots

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/s/

GINA M DAVIS
12/22/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207981

LATE-CYCLE MEETING MINUTES

Taiho Oncology, Inc.
Attention: Lisa Cooper, Ph.D.
Associate Director, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Cooper:

Please refer to your New Drug Application (NDA) dated December 19, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lonsurf (trifluridine and tipiracil), 15 mg and 20 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on September 18, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Gina Davis, Regulatory Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Steve Lemery, M.D.
Cross-Discipline Team Lead
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: September 18, 2015
Meeting Location: CDER WO 22 – Room 1311
Application Number: NDA 207981
Product Name: Lonsurf (trifluridine and tipiracil)
Applicant Name: Taiho Oncology, Inc.
Meeting Chair: Steven Lemery, M.D.
Meeting Recorder: Gina Davis, M.T.

FDA ATTENDEES

Eric C. Benn, President and CEO
Fabio Benedetti, Chief Medical Officer
Lieselotte Bloss, Regulatory Affairs
Lisa Cooper, Regulatory Affairs
Muriel Anselmi, Regulatory Affairs, Servier
Rachel Mathew, Regulatory Affairs CMC
Robert Winkler, Research and Development

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou

APPLICANT ATTENDEES

Richard Pazdur, M.D., Director, Office of Hematology and Oncology Products
Patricia Keegan, M.D., Director, Division of Oncology Products 2 (DOP 2)
Steven Lemery, M.D., Cross-Discipline Team Lead, DOP 2
Leigh Marcus, M.D., Medical Officer, DOP 2
Gina Davis, M.T., Regulatory Project Manager, DOP 2
Sachia Khasar, Ph.D., Nonclinical Reviewer, Division of Hematology Oncology Toxicology
X. Cao, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology V (D CPV)
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, DCP V
Olen Stephens, Ph.D., Branch Chief, Office of Product Quality/Office of New Drug Products
Latoria Ford, BSN, MA, Regulatory Project Manager, Office of Surveillance and Epidemiology

1.0 BACKGROUND

On September 14, 2015, DOP 2 sent Taiho Oncology, Inc. (Taiho) the Late Cycle Meeting Package for the Lonsurf marketing application as well as their counter-proposal to the Lonsurf PI. Taiho agreed with the counter-proposal regarding the Lonsurf PI on September 15, 2015. FDA will discuss the next steps of the process with Taiho at the Late Cycle Meeting.

Proposed indication: For the treatment of patients with metastatic colorectal cancer who have been previously treated with, [REDACTED] ^{(b) (4)} fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy”

PDUFA goal date: December 19, 2015

FDA issued a Background Package in preparation for this meeting on September 14, 2015.

2.0 DISCUSSION

On September 18, 2015, DOP 2 met with Taiho and stated that that there appeared to be no remaining issues and that final reviews were being completed. FDA informed Taiho that it was possible that additional edits to the label could be forthcoming and recommended that Taiho review any possible changes as soon as possible to facilitate the action on the application.

3.0 ACTION

Taiho had no questions or comments and would wait to hear from the Division.

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/s/

STEVEN J LEMERY
09/22/2015



NDA 207981

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Taiho Oncology, Inc.
Attention: Lisa Cooper, Ph.D.
Associate Director, Regulatory Affairs
202 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Cooper:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lonsurf (trifluridine and tipiracil), 15 mg and 20 mg tablets.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 18, 2015.
Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Gina Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Friday, September 18, 2015, 11:00 AM – 12:00 PM
Meeting Location: WO Building 22, Room 1315

Application Number: NDA 207981
Product Name: Lonsurf (trifluridine and tipiracil)
Indication: For the treatment of metastatic colorectal cancer
Sponsor/Applicant Name: Taiho Oncology, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters will be issued.

2. Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes: Welcome, Introductions, Ground rules, Objectives
2. Discuss proposed Postmarketing Requirements/Postmarketing Commitments – 5 minutes
 - a. 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.”

Final Protocol Submission:	Submitted
Study/Trial Completion:	09/2017
Final Report Submission:	12/2017
 - b. Complete the ongoing pharmacokinetic trial to determine an appropriate dose of Lonsurf in patients with severe hepatic 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.”

Final Protocol Submission:	Submitted
Study/Trial Completion:	09/2017
Final Report Submission:	12/2017
3. Discuss major labeling issues – 30 minutes

Taiho or FDA may elect to take this time to discuss any issues associated with the package insert and the patient package insert. FDA sent labeling to Taiho on August 19, 2015, and Taiho provide responses to FDA’s proposed labeling via electronic (email) communication on August 26, 2015 and as a formal amendment to the application on August 31, 2015. FDA reviewed Taiho’s counter-proposal and sent a response on September 14, 2015, proposing edits to the package insert and the patient package insert.
4. FDA to discuss current review plans –5 minutes
5. Wrap-up and Action Items – 5 minutes

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/s/

PATRICIA KEEGAN
09/14/2015