CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207981Orig1s012

Trade Name:	LONSURF
Generic or Proper Name:	trifluridine and tipiracil
Sponsor:	Taiho Oncology, Inc.
Approval Date:	August 2, 2023
Indication:	Lonsurf is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with: • metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. • metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 207981/S-012

SUPPLEMENT APPROVAL

Taiho Oncology, Inc.
Attention: Sok Kang, PharmD
Director, Regulatory Affairs Strategy
101 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Dr. Kang:

Please refer to your February 13, 2023, supplemental new drug application (sNDA), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lonsurf (trifluridine/tipiracil).

This Prior Approval supplemental new drug application provides for updates to the Lonsurf Prescribing Information (PI) and Patient Package Insert based on data from Protocol CL3-95005-007, entitled, "An Open Label, Randomised, Phase III Study Comparing Trifluridine/Tipiracil in Combination with Bevacizumab to Trifluridine/Tipiracil Monotherapy in Patients with Refractory Metastatic Colorectal Cancer (SUNLIGHT study)" for the following new indication:

> *LONSURF, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.*

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for this application because necessary studies are impossible or highly impracticable.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

Sincerely,

{See appended electronic signature page}

`Lola Fashoyin-Aje, MD, MPH
Deputy Director
Division of Oncology 3
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IBILOLA A FASHOYIN-AJE
08/02/2023 10:55:55 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LONSURF safely and effectively. See full prescribing information for LONSURF.

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.1)	8/2023
Dosage and Administration (2)	8/2023
Warnings and Precaution (5.1)	8/2023

INDICATIONS AND USAGE

LONSURF is a combination of trifluridine, a nucleoside metabolic inhibitor, and tipiracil, a thymidine phosphorylase inhibitor, indicated for the treatment of adult patients with:

- metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. (1.1)
- metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy. (1.2)

DOSAGE AND ADMINISTRATION

- Recommended Dosage: 35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil (3)
- 20 mg trifluridine/8.19 mg tipiracil (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Severe Myelosuppression: Obtain complete blood counts prior to and on Day 15 of each cycle. Withhold and resume at next lower LONSURF dosage as recommended. (2.1, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions or laboratory abnormalities for single agent LONSURF (≥10%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. (6.1)
The most common adverse reactions or laboratory abnormalities for LONSURF in combination with bevacizumab (≥20%) are neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taiho Oncology, Inc. at 1-844-878-2446 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Geriatric Use: For LONSURF as a single agent, Grade 3 or 4 neutropenia, Grade 3 anemia and Grade 3 or 4 thrombocytopenia occurred more commonly in patients 65 years or older. (8.5) For LONSURF in combination with bevacizumab Grade 3 or 4 neutropenia and Grade 3 or 4 thrombocytopenia occurred more commonly in patients 65 years or older. (8.5)
- Hepatic Impairment: Do not initiate LONSURF in patients with baseline moderate or severe hepatic impairment. (8.7)
- Renal Impairment: Reduce LONSURF dose in patients with severe renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 8/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

LONSURF, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2 Metastatic Gastric Cancer

LONSURF is indicated for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of LONSURF as a single agent or in combination with bevacizumab is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. Round dose to the nearest 5 mg increment.

Refer to the Prescribing Information for bevacizumab dosing information.

Instruct patients to swallow LONSURF tablets whole.

Instruct patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Table 1 shows the calculated initial daily dose based on body surface area (BSA).

Table 1: Recommended Dosage According to Body Surface Area (BSA)

BSA (m2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg	20 mg
< 1.07	70	35	1	1
1.07 – 1.22	80	40	0	2
1.23 – 1.37	90	45	3	0
1.38 – 1.52	100	50	2	1
1.53 – 1.68	110	55	1	2
1.69 – 1.83	120	60	0	3
1.84 – 1.98	130	65	3	1
1.99 – 2.14	140	70	2	2
2.15 - 2.29	150	75	1	3
≥2.30	160	80	0	4

2.2 Dosage Modifications for Adverse Reactions

Obtain complete blood cell counts prior to and on Day 15 of each cycle *[see Warnings and Precautions (5.1)]*.

Do not initiate the cycle of LONSURF until:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3 or febrile neutropenia is resolved
- Platelets greater than or equal to 75,000/mm^3
- Grade 3 or 4 non-hematological adverse reactions are resolved to Grade 0 or 1

Within a treatment cycle, withhold LONSURF for any of the following:

- Absolute neutrophil count (ANC) less than 500/mm^3 or febrile neutropenia
- Platelets less than 50,000/mm^3
- Grade 3 or 4 non-hematologic adverse reaction

After recovery, resume LONSURF after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur:

- Febrile neutropenia
- Uncomplicated Grade 4 neutropenia (which has recovered to greater than or equal to 1,500/mm^3) or thrombocytopenia (which has recovered to greater than or equal to 75,000/mm^3) that results in more than 1 week delay in start of next cycle

- Non-hematologic Grade 3 or Grade 4 adverse reaction except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication

A maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily. Do not escalate LONSURF dosage after it has been reduced.

Refer to the bevacizumab prescribing information for dose modifications for adverse reactions associated with bevacizumab.

2.3 Recommended Dosage for Renal Impairment

Severe Renal Impairment

In patients with severe renal impairment [creatinine clearance (CLcr) of 15 to 29 mL/min as determined by the Cockcroft-Gault formula], the recommended dosage is 20 mg/m^2 (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle (Table 2) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Reduce dose to 15 mg/m^2 twice daily in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2 twice daily (Table 2). Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.

Table 2: Recommended Dosage for Severe Renal Impairment According to BSA

BSA (m^2)	Total daily dose (mg)	Dose (mg) administered twice daily	Tablets per dose	
			15 mg	20 mg
For a dose of 20 mg/m^2 twice daily:				
< 1.14	40	20	0	1
1.14 – 1.34	50	25*	2 in the evening*	1 in the morning*
1.35 – 1.59	60	30	2	0
1.60 – 1.94	70	35	1	1
1.95 – 2.09	80	40	0	2
2.10 – 2.34	90	45	3	0
≥ 2.35	100	50	2	1
For a dose of 15 mg/m^2 twice daily:				
< 1.15	30	15	1	0
1.15 – 1.49	40	20	0	1
1.50 – 1.84	50	25*	2 in the evening*	1 in the morning*
1.85 – 2.09	60	30	2	0
2.10 – 2.34	70	35	1	1
≥ 2.35	80	40	0	2

* For a total daily dose of 50 mg, instruct patients to take 1 x 20-mg tablet in the morning and 2 x 15-mg tablets in the evening.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 15 mg trifluridine/6.14 mg tipiracil: white, biconvex, round, film-coated, imprinted with ‘15’ on one side, and ‘102’ and ‘15 mg’ on the other side, in gray ink.
- 20 mg trifluridine/8.19 mg tipiracil: pale red, biconvex, round, film-coated, imprinted with ‘20’ on one side, and ‘102’ and ‘20 mg’ on the other side, in gray ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In the 1114 patients who received LONSURF as a single agent, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (38%), anemia (17%), thrombocytopenia (4%) and febrile neutropenia (3%). Three patients (0.3%) died due to neutropenic infection/sepsis; four other patients (0.5%) died due to septic shock. A total of 14% of patients received granulocyte-colony stimulating factors.

In the 246 patients who received LONSURF in combination with bevacizumab, LONSURF caused severe or life-threatening myelosuppression (Grade 3-4) consisting of neutropenia (52%), anemia (5%), thrombocytopenia (4%) and febrile neutropenia (0.4%). One patient (0.4%) died due to abdominal sepsis and two other patients (0.8%) died due to septic shock. A total of 29% of patients received granulocyte-colony stimulating factors. Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for severe myelosuppression and resume at the next lower dosage *[see Dosage and Administration (2.2)]*.

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dosage levels resulting in exposures lower than those achieved at the recommended dosage of 35 mg/m^2 twice daily. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with LONSURF and for at least 6 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe Myelosuppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to LONSURF at the recommended dose in 533 patients with metastatic colorectal cancer in RECOURSE, 246 patients with metastatic colorectal cancer treated with LONSURF as monotherapy in SUNLIGHT and 335 patients with metastatic gastric cancer in TAGS. Among the 1114 patients who received LONSURF as a single agent, 12% were exposed for 6 months or longer and 1% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥10%) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

Among the 246 patients with metastatic colorectal cancer treated with LONSURF in combination with bevacizumab in SUNLIGHT, 39% were exposed for 6 months or longer, and 14% were exposed for 12 months or longer. The most common adverse reactions or laboratory abnormalities (≥20%) were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased AST, increased ALT, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite.

Metastatic Colorectal Cancer

LONSURF as a single agent

The safety of LONSURF was evaluated in RECOURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer *[see Clinical Studies (14.1)]*. Patients received LONSURF 35 mg/m^2/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. In RECOURSE, 12% of patients received LONSURF for more than 6 months and 1% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years; 61% male; 57% White, 35% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In RECOURSE, 3.6% of patients discontinued LONSURF for an adverse reaction and 14% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 3 and Table 4 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in RECOURSE.

Table 3: Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in RECOURSE

Adverse Reactions	LONSURF (N=533)		Placebo (N=265)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
General				
Asthenia/fatigue	52	7	35	9
Pyrexia	19	1.3	14	0.4
Gastrointestinal				
Nausea	48	1.9	24	1.1
Diarrhea	32	3	12	0.4
Vomiting	28	2.1	14	0.4
Abdominal pain	21	2.4	19	3.8
Stomatitis	8	0.4	6	0
Metabolism and nutrition				
Decreased appetite	39	3.6	29	4.9
Infections†	27	7	16	4.9
Nervous system				
Dysgeusia	7	0	2.3	0
Skin and subcutaneous tissue				
Alopecia	7	0	1.1	0

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology
†Incidence reflects 64 preferred terms in the Infections and Infestations system organ class.

Table 4: Select Laboratory Abnormalities in RECOURSE

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Anemia†	77	18	33	3
Neutropenia	67	38	0.8	0
Thrombocytopenia	42	5	8	0.4

* Worst Grade at least one grade higher than baseline, with percentages based on number of patients with post-baseline samples, which may be <533 (LONSURF) or 265 (placebo)
† One Grade 4 anemia adverse reaction based on clinical criteria was reported

In RECOURSE, pulmonary emboli occurred more frequently in LONSURF-treated patients (2%) compared to no patients on placebo.

LONSURF in combination with bevacizumab

The safety of LONSURF in combination with bevacizumab was evaluated in SUNLIGHT, an international, randomized, open label study in patients with previously treated metastatic colorectal cancer *[see Clinical Studies (14.1)]*.

The study population characteristics were: median age 63 years (20 to 90 years); 52% male; 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown; and baseline ECOG performance status 0 (46%), 1 (54%), or 2 (0.2%).

Serious adverse reactions occurred in 25% of patients. The most frequent serious adverse reactions (≥2%) were intestinal obstruction (2.8%), and COVID-19 (2%). Fatal adverse reactions occurred in 1.2% of patients who received LONSURF in combination with bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).

Permanent treatment discontinuation due to an adverse reaction occurred in 13% of patients. The adverse reaction which resulted in permanent treatment discontinuation in ≥2% of patients was fatigue.

Dosage reductions due to an adverse reaction or laboratory abnormality occurred in 7% of patients. At least one dose reduction in 3.7% of patients was required for neutropenia.

Dosage interruptions due to an adverse reaction occurred in 11% of patients who received LONSURF in combination with bevacizumab. The adverse reaction that required dosage interruption in ≥2% of patients was nausea.

The most common adverse reactions or laboratory abnormalities (≥20% in incidence) in patients treated with LONSURF in combination with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. Table 5 and Table 6 list the adverse reactions and laboratory abnormalities, respectively, observed in SUNLIGHT.

Table 5: Adverse Reactions (≥5%) in SUNLIGHT

Adverse Reactions	LONSURF + Bevacizumab (N=246) (%)		LONSURF (N=246) (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				
Nausea	37	1.6	27	1.6
Diarrhea*	21	1.2	19	2.4
Abdominal pain*	20	2.8	18	3.7
Vomiting*	19	0.8	15	1.6
Stomatitis*	13	<0.4	4.1	0
Constipation	11	0	11	0.8
General disorders and administration site conditions				
Fatigue*	45	5	37	8
Pyrexia	4.9	0	6	0.4
Infections and infestations*	31	8	24	8
Metabolism and nutrition disorders				
Decreased appetite	20	<0.8	15	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	18	1.2	11	2
Nervous system disorder				
Headache	8	0	3.7	0
Vascular disorders				
Hypertension*	11	6	2	1.2
Hemorrhage*	10	1.2	3.7	0.8
Renal and urinary disorders				
Proteinuria	6	0.8	1.2	0

*Represents a composite of multiple related terms

Table 6: Select Laboratory Abnormalities (≥10%) in SUNLIGHT

Laboratory parameters	LONSURF + Bevacizumab[a]		LONSURF[a]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Neutrophils decreased	80	52	68	39
Hemoglobin decreased	68	5	73	11
Platelets decreased	54	4.1	29	0.8
Chemistry				
Aspartate aminotransferase increased	34	2.1	28	1.2
Alanine aminotransferase increased	33	3.3	23	0.4
Alkaline phosphatase increased	31	0.8	36	1.2
Sodium decreased	25	2.1	20	3.3
Potassium increased	17	0	15	0
Potassium decreased	12	0.8	12	2.5
Creatinine increased	12	0.8	15	0

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: LONSURF + bevacizumab group (n=242 patients) and LONSURF group (range: 240 to 242 patients).

Metastatic Gastric Cancer

The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double-blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease *[see Clinical Studies (14.2)]*. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Patients received LONSURF 35 mg/m^2/dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. In TAGS, 10% of patients received LONSURF for more than 6 months and 0.9% of patients received LONSURF for more than 1 year.

The study population characteristics were: median age 63 years (24 to 89 years); 73% male; 70% White, 16% Asian, and 1% Black.

The most common adverse reactions or laboratory abnormalities (≥10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.

In TAGS, 13% of patients discontinued LONSURF for an adverse reaction and 11% of patients required a dose reduction. The most common adverse reactions or laboratory abnormalities leading to dose reduction were neutropenia, anemia, febrile neutropenia, and diarrhea.

Table 7 and Table 8 list the adverse reactions and laboratory abnormalities (graded using CTCAE v4.03), respectively, observed in TAGS.

Table 7: Adverse Reactions (≥5%) in Patients Receiving LONSURF and at a Higher Incidence (>2%) than in Patients Receiving Placebo in TAGS

Adverse Reactions	LONSURF (N=335)		Placebo (N=168)	
	All Grades (%)	Grades 3-4* (%)	All Grades (%)	Grades 3-4* (%)
Gastrointestinal				
Nausea	37	3	32	3
Vomiting	25	4	20	2
Diarrhea	23	3	14	2
Metabolism and nutrition				
Decreased appetite	34	9	31	7
Infections†	23	5	16	5

*No Grade 4 definition for nausea or fatigue in NCI CTCAE, version 4.03.
†Incidence reflects 46 preferred terms in the Infections and Infestations system organ class.

Table 8: Laboratory Abnormalities in TAGS

Laboratory Parameter*	LONSURF		Placebo	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematologic				
Neutropenia	66	38	4	0
Anemia†	63	19	38	7
Thrombocytopenia	34	6	9	0

* Worst Grade at least one Grade higher than baseline, with percent based on number of patients with post-baseline samples which may be <335 (LONSURF) or 168 (placebo)
† Anemia: No Grade 4 definition in CTCAE, v4.03

In TAGS, pulmonary emboli occurred more frequently in LONSURF-treated patients (3.1%) compared to 1.8% for patients on placebo.

Additional Clinical Experience

Interstitial lung disease was reported in 15 (0.2%) patients, 3 of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action *[see Clinical Pharmacology (12.2)]*, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to human exposures at the recommended clinical dose (see Data). There are no available data on LONSURF use in pregnant women. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

There are no data on the presence of trifluridine, tipiracil or its metabolites in human milk or its effects on the breastfed child or on milk production. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk *(see Data)*. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose.

Data

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating LONSURF *[see Use in Specific Populations (8.1)]*.

Contraception

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

Females

Advise females of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose.

Males

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

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Juvenile Animal Toxicity Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses ≥ 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m^2 twice daily).

8.5 Geriatric Use

Of the 1114 patients with metastatic colorectal cancer or gastric cancer who received single agent LONSURF in clinical studies, 45% were 65 years of age or over, and 11% were 75 and over. In the 246 patients who received LONSURF in combination with bevacizumab; 41% were 65 years of age or over, and 10% were 75 and over. While these studies were not designed to detect a difference in efficacy, no overall differences were observed in patients 65 or older versus younger patients with either LONSURF as a single agent or LONSURF in combination with bevacizumab.

Patients 65 years of age or older who received LONSURF as a single agent had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (46% vs 32%), Grade 3 anemia (20% vs 14%), and Grade 3 or 4 thrombocytopenia (6% vs 3%). Patients 65 years of age or older who received LONSURF in combination with bevacizumab had a higher incidence of the following hematologic laboratory abnormalities compared to patients younger than 65 years: Grade 3 or 4 neutropenia (60% vs 46%) and Grade 3 or 4 thrombocytopenia (5% vs 4%).

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) *[see Dosage and Administration (2.3)]*. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

8.7 Hepatic Impairment

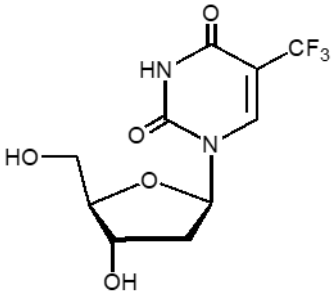
No adjustment to the starting dosage of LONSURF is recommended for patients with mild hepatic impairment. Do not initiate LONSURF in patients with baseline moderate or severe (total bilirubin >1.5 times ULN and any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

LONSURF contains trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5.

Trifluridine

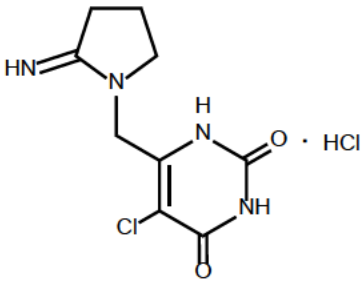
Trifluridine, a nucleoside metabolic inhibitor, is described chemically as 2'-deoxy-5-(trifluoromethyl) uridine and has the following structural formula:



Trifluridine has a molecular formula $C_{10}H_{11}F_3N_2O_5$ and a molecular weight of 296.20. Trifluridine is a white crystalline powder, soluble in water, ethanol, 0.01 mol/L hydrochloric acid, 0.01 mol/L sodium hydroxide solution; freely soluble in methanol, acetone; sparingly soluble in 2-propanol, acetonitrile; slightly soluble in diethyl ether; and very slightly soluble in isopropyl ether.

Tipiracil hydrochloride

Tipiracil hydrochloride, a thymidine phosphorylase inhibitor, is described chemically as 5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2,4-(1*H*,3*H*)-dione monohydrochloride or 2,4(1*H*,3*H*)-Pyrimidinedione, 5-chloro-6-[(2-imino-1-pyrrolidinyl)methyl]-, hydrochloride (1:1) and has the following structural formula:



Tipiracil hydrochloride has a molecular formula $C_9H_{11}ClN_4O_2$•HCl and a molecular weight of 279.12. Tipiracil hydrochloride is a white crystalline powder, soluble in water, 0.01 mol/L hydrochloric acid, and 0.01 mol/L sodium hydroxide; slightly soluble in methanol; very slightly soluble in ethanol; and practically insoluble in acetonitrile, 2-propanol, acetone, diisopropyl ether, and diethyl ether.

LONSURF (trifluridine and tipiracil) tablets for oral use contain 15 mg of trifluridine and 6.14 mg of tipiracil equivalent to 7.065 mg of tipiracil hydrochloride or 20 mg of trifluridine and 8.19 mg of tipiracil equivalent to 9.420 mg of tipiracil hydrochloride.

LONSURF tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate. The tablets are imprinted with ink containing shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LONSURF consists of a thymidine-based nucleoside analog, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Inclusion of tipiracil increases trifluridine exposure by inhibiting its metabolism by thymidine phosphorylase.

Following uptake into cancer cells, trifluridine is incorporated into DNA, interferes with DNA synthesis and inhibits cell proliferation. Trifluridine/tipiracil demonstrated anti-tumor activity against *KRAS* wild-type and mutant human colorectal cancer xenografts in mice.

12.2 Pharmacodynamics

Cardiac Electrophysiology

LONSURF administered to 42 patients with advanced solid tumors at the recommended dosage had no large effect (i.e. >20 ms) in the mean QTc interval when compared to placebo and no exposure-QT relationship was identified. Two of 42 patients (4.8%) had QTc >500 msec and 2.4% had a QTc increase from baseline >60 msec.

12.3 Pharmacokinetics

After twice daily dosing of LONSURF, systemic exposure (AUC) of trifluridine increased more than dose-proportionally over the dose range of 15 mg/m^2 (0.43 times the recommended dose) to 35 mg/m^2.

The accumulation of trifluridine was 3-fold for $AUC_{0\text{-}12hr}$ and 2-fold for C_{max} at steady state while no accumulation was observed for tipiracil.

Administration of a single dose of LONSURF 35 mg/m^2 increased the mean $AUC_{0\text{-}last}$ of trifluridine by 37-fold and C_{max} by 22-fold with reduced variability compared to administration of a single dose of trifluridine 35 mg/m^2 alone.

Absorption

Following a single oral administration of LONSURF at 35 mg/m^2 in patients with cancer, the mean time to peak plasma concentration (T_{max}) of trifluridine was around 2 hours.

Food Effect

A standardized high-fat, high-calorie meal decreased trifluridine C_{max}, tipiracil C_{max} and AUC by approximately 40%, but did not change trifluridine AUC compared to those in a fasting state in patients with cancer following administration of a single dose of LONSURF 35 mg/m^2.

Distribution

Trifluridine mainly binds to human serum albumin. The in vitro protein binding of trifluridine in human plasma is >96%, independent of drug concentration and presence of tipiracil. Plasma protein binding of tipiracil is below 8%.

Elimination

After administration of LONSURF 35 mg/m^2, the mean elimination half-life ($t_{1/2}$) of trifluridine was 1.4 hours and of tipiracil was 2.1 hours after a single dose. The mean elimination half-life at steady state of trifluridine was 2.1 hours and of tipiracil was 2.4 hours.

Metabolism

Trifluridine and tipiracil are not metabolized by cytochrome P450 (CYP) enzymes. Trifluridine is mainly eliminated by metabolism via thymidine phosphorylase to form an inactive metabolite, 5-(trifluoromethyl) uracil (FTY). No other major metabolites were detected in plasma or urine.

Excretion

After single oral administration of LONSURF (60 mg) with [^{14}C]-trifluridine, the total cumulative excretion of radioactivity was 60% of the administered dose. The majority of recovered radioactivity was eliminated into urine (55% of the dose) as FTY and trifluridine glucuronide isomers within 24 hours and the excretion into feces and expired air was <3% for both. The unchanged trifluridine was <3% of administered dose recovered in the urine and feces.

After single oral administration of LONSURF (60 mg) with [^{14}C]-tipiracil hydrochloride, recovered radioactivity was 77% of the dose, which consisted of 27% urinary excretion and 50% fecal excretion. Tipiracil was the major component and 6-HMU was the major metabolite in urine, and feces.

Specific Populations

Based on the population pharmacokinetic analysis, there is no clinically relevant effect of age, sex, or race (White or Asian) on the pharmacokinetics of trifluridine or tipiracil.

Patients with Renal Impairment

In a dedicated renal impairment study, all patients received LONSURF 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state $AUC_{0\text{-last}}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90 mL/min). Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-last}}$ of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

Patients with Hepatic Impairment

No clinically important differences in the mean exposures of trifluridine and tipiracil were observed between patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin <1 to 1.5 times ULN and any AST) to moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST) and patients with normal hepatic function (total bilirubin and AST ≤ ULN); however, 5 of 6 patients with moderate hepatic impairment experienced Grade 3 or 4 increased bilirubin levels. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe hepatic impairment *[see Dosage Modifications (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

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

In vitro studies indicated that trifluridine was not an inhibitor of or substrate for human uptake and efflux transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies evaluating the carcinogenic potential of trifluridine/tipiracil in animals have been performed. Trifluridine/tipiracil was genotoxic in a reverse mutation test in bacteria, a chromosomal aberration test in mammalian-cultured cells, and a micronucleus test in mice.

Animal studies did not indicate an effect of trifluridine/tipiracil on male fertility in rats. Dose-related increases in the corpus luteum count and implanted embryo count were observed, but female fertility was not affected.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

Previously treated metastatic colorectal cancer (single agent LONSURF)

RECOURSE

The efficacy of LONSURF was evaluated in RECOURSE (NCT01607957), an international, randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic colorectal cancer (mCRC). Key eligibility criteria included prior treatment with at least 2 lines of standard chemotherapy for metastatic CRC, ECOG performance status (PS) 0-1, absence of brain metastasis, and absence of ascites requiring drainage in the past four weeks. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 or matching placebo orally twice daily after meals on Days 1-5 and 8-12 of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by KRAS status (wild-type vs. mutant), time since diagnosis of first metastasis (<18 months vs. ≥ 18 months), and region (Japan vs. US, Europe and Australia). The major efficacy outcome measure was overall survival (OS) and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 800 patients were randomized to LONSURF (N=534) with best supportive care (BSC) or matching placebo (N=266) plus BSC. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PS of 0 or 1. The primary site of disease was colon (62%) or rectum (38%). KRAS status was wild-type (49%) or mutant (51%) at study entry. All patients received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. All but one patient received bevacizumab and all but two patients with KRAS wild-type tumors received panitumumab or cetuximab.

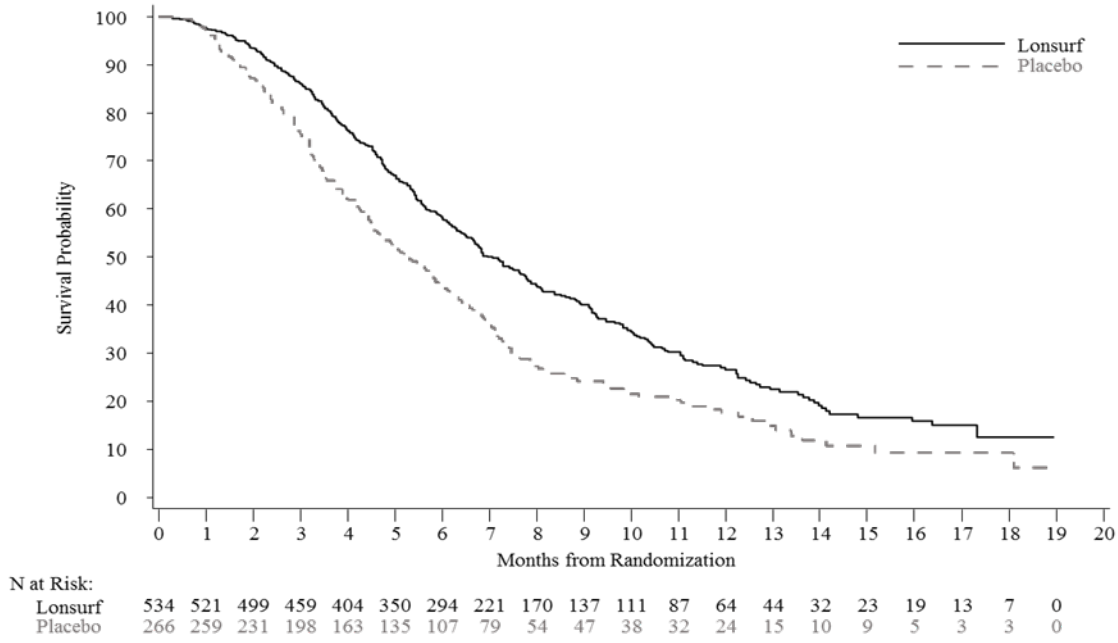
Efficacy results are summarized in Table 9 and Figure 1.

Table 9: Efficacy Results from RECOURSE

	LONSURF (N=534)	**Placebo (N=266)**
Overall Survival		
Number of deaths, N (%)	364 (68)	210 (79)
Median OS (months)[a] (95% CI)[b]	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)
Hazard ratio (95% CI)	0.68 (0.58, 0.81)	
p-value[c]	<0.001	
Progression-Free Survival		
Number of events, N (%)	472 (88)	251 (94)
Hazard ratio (95% CI)	0.47 (0.40, 0.55)	
p-value[c]	<0.001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region), 2-sided

Figure 1: Kaplan-Meier Curves of Overall Survival in RECOURSE



Previously treated metastatic colorectal cancer (LONSURF in combination with bevacizumab)

SUNLIGHT

The efficacy of LONSURF in combination with bevacizumab was evaluated in SUNLIGHT (NCT 04737187), an international, randomized (1:1), open label study in patients with previously treated metastatic colorectal cancer. Patients were required to have received no more than 2 prior treatments for advanced disease, including a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (optional) and an anti-EGFR monoclonal antibody for patients with RAS wild-type. Other key eligibility criteria included ECOG performance status (PS) 0-1, absence of symptomatic brain metastases, absence of ascites requiring drainage in the past 4 weeks, absence of uncontrolled hypertension, absence of non-healing wound, and absence of deep venous thromboembolic event in the past 4 weeks. Patients were randomized to receive LONSURF 35 mg/m^2 administered orally twice daily on Days 1 to 5 and 8 to 12 of each 28-day cycle with or without bevacizumab 5 mg/kg administered intravenously every 2 weeks (on Day 1 and Day 15) of each 4-week cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America, European Union, Rest of the World), time since diagnosis of metastatic disease (<18 months, ≥18 months) and RAS status (wild-type, mutant). The major efficacy outcome was overall survival (OS), and an additional efficacy outcome measure was progression-free survival (PFS).

A total of 492 patients were randomized to receive LONSURF in combination with bevacizumab (N=246) or LONSURF as a single agent (N=246). The trial population characteristics were as follows: median age 63 years, 52% male, 88% White, 1.4% Black, 0.2% Asian, 0.2% American Indian or Alaska Native, and 9.6% were unknown, 46% had ECOG PS 0 and 54% had ECOG PS 1. The primary site of disease was colon (73%) or rectum (27%). Seventy-one percent of patients had a RAS mutant status. A total of 92% of patients received 2 prior anticancer treatment

regimens for advanced CRC; all patients received prior fluoropyrimidine; 99.8% of patients received prior irinotecan; 98% of patients received prior oxaliplatin. Among all 492 treated patients, 76% received prior anti-VEGF treatment, and 72% received an anti-VEGF monoclonal antibody. Among the 142 patients with RAS wild-type mCRC, 94% received prior anti-EGFR monoclonal antibody.

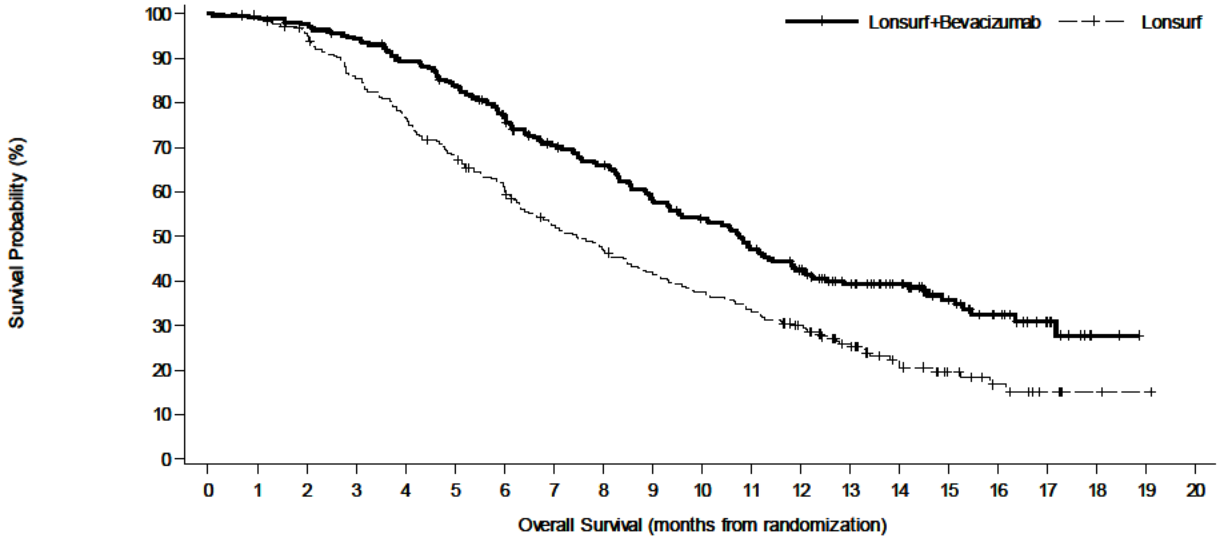
Efficacy results are summarized in Table 10 and Figure 2.

Table 10: Efficacy Results from SUNLIGHT

	LONSURF plus Bevacizumab (N=246)	**LONSURF (N=246)**
Overall survival		
Number of deaths, N (%)	148 (60)	183 (74)
Median OS (months)[a] (95% CI)[b]	10.8 (9.4, 11.8)	7.5 (6.3, 8.6)
Hazard ratio (95% CI)[c]	0.61 (0.49, 0.77)	
p-value[d]	<0.001	
Progression-free survival (per investigator)		
Number of events N (%)	206 (84)	236 (96)
Median PFS (months)[a] (95% CI)[b]	5.6 (4.5, 5.9)	2.4 (2.1, 3.2)
Hazard ratio (95% CI)[d]	0.44 (0.36, 0.54)	
p-value[d]	<0.001	

a Kaplan-Meier estimates
b Methodology of Brookmeyer and Crowley
c Stratified proportional hazards model (strata: region, time since first metastasis diagnosis, RAS status)
d Stratified log-rank test (strata: region, time since first metastasis diagnosis, RAS status), 1-sided p-value

Figure 2: Kaplan-Meier Curves of Overall Survival in SUNLIGHT



Number of patients at risk:

Lonsurf+Bevacizumab	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
Lonsurf	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

14.2 Metastatic Gastric Cancer

The efficacy of LONSURF was evaluated in TAGS (NCT02500043), an international, randomized, double-blind, placebo-controlled study in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least 2 prior regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Other key eligibility criteria included ECOG performance status (PS) 0 or 1. Patients were randomized 2:1 to receive LONSURF 35 mg/m^2 orally twice daily on Days 1-5 and 8-12 of each 28-day cycle with best supportive care (BSC) or matching placebo with BSC until disease progression or unacceptable toxicity. Randomization was stratified by ECOG PS at baseline (0 vs. 1), prior ramucirumab (yes vs. no), and geographic region (Japan vs. rest of world). The major efficacy outcome measure was OS and an additional outcome measure was PFS.

A total of 507 patients were randomized to LONSURF (N=337) or placebo (N=170). The median age was 63 years, 73% were male, 70% and 16% were White and Asian respectively, and 38% had a baseline ECOG PS of 0. Seventy-one percent of patients had gastric tumors, 29% had GEJ tumors, and two patients had gastric/GEJ tumors. All patients received platinum-based chemotherapy, 99% received fluoropyrimidine-based therapy, 91% received a taxane, 55% received irinotecan, and 33% received ramucirumab. The HER2 status was negative in 62%,

positive in 19%, and unknown in 20% of patients. Among the 94 patients with HER2 positive tumors, 89% received prior anti-HER2 therapy.

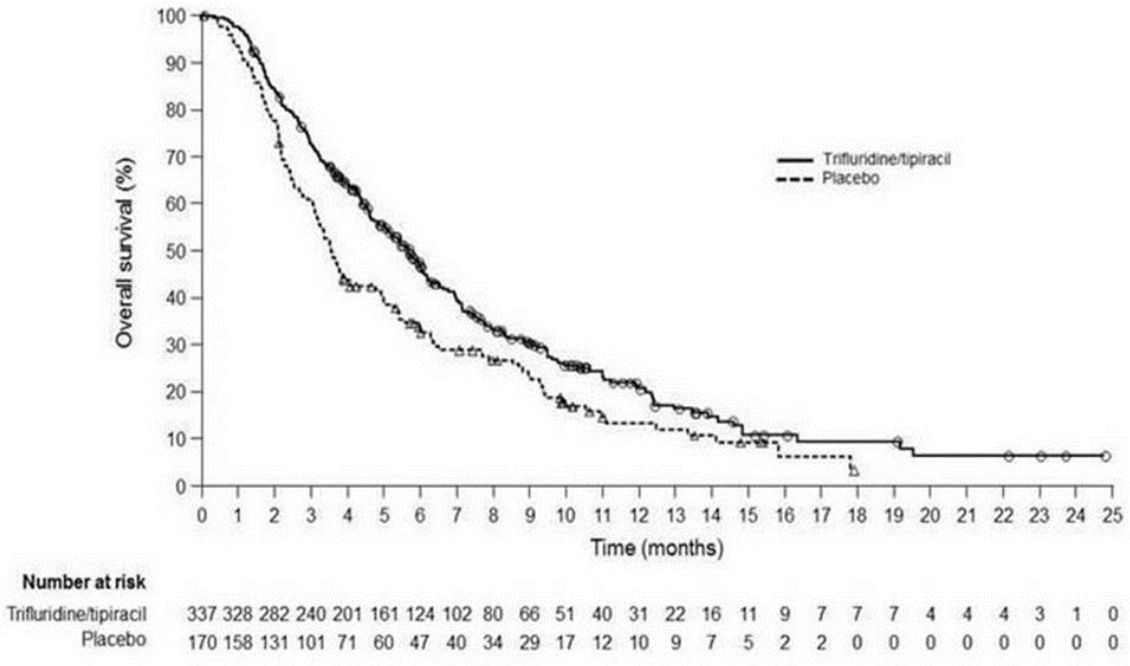
Efficacy results are summarized in Table 11 and Figure 3.

Table 11: Efficacy Results from TAGS

	LONSURF (N=337)	Placebo (N=170)
Overall Survival		
Number of deaths, N (%)	244 (72)	140 (82)
Median OS (months)[a] (95% CI)[b]	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
Hazard ratio (95% CI)	0.69 (0.56, 0.85)	
p-value[c]	0.0006	
Progression-Free Survival		
Number of events, N (%)	287 (85)	156 (92)
Hazard ratio (95% CI)	0.56 (0.46, 0.68)	
p-value[c]	<0.0001	

[a] Kaplan-Meier estimates
[b] Methodology of Brookmeyer and Crowley
[c] Stratified log-rank test (strata: ECOG PS, prior ramucirumab treatment, region), 2-sided

Figure 3: Kaplan-Meier Curves of Overall Survival in TAGS



15 REFERENCES

1. "OSHA Hazardous Drugs". OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

LONSURF 15 mg/6.14 mg tablets are supplied as white, biconvex, round, film-coated tablet, imprinted with '15' on one side, and '102' and '15 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1025-1
- 40 count: NDC 64842-1025-2
- 60 count: NDC 64842-1025-3

LONSURF 20 mg/8.19 mg tablets are supplied as pale red, biconvex, round, film-coated tablet, imprinted with '20' on one side, and '102' and '20 mg' on the other side, in gray ink. The tablets are packaged in HDPE bottles with child resistant closures in the following presentations:

- 20 count: NDC 64842-1020-1
- 40 count: NDC 64842-1020-2
- 60 count: NDC 64842-1020-3

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

LONSURF is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

If stored outside of original bottle, discard after 30 days.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Myelosuppression

Advise patients to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Toxicity

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain *[see Adverse Reactions (6.1)]*.

Administration Instructions

Advise patients that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dosage.

Advise patients to take LONSURF with food *[see Dosage and Administration (2.1)]*.

Advise patients not to retake doses of LONSURF that are vomited or missed and to continue with the next scheduled dose.

Advise patients that anyone else who handles their medication should wear gloves *[see References (15)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise female patients of reproductive potential to use effective contraception during treatment with LONSURF and for at least 6 months after the final dose *[see Warnings and Precautions (5.2), Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with LONSURF and for 1 day following the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan

Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd. used under license by Taiho Oncology, Inc.

PATIENT INFORMATION
LONSURF® (LON-serf)
(trifluridine and tipiracil)
tablets

What is the most important information I should know about LONSURF?

Your healthcare provider should do blood tests before you receive LONSURF, at day 15 during treatment with LONSURF, and as needed to check your blood cell counts.

LONSURF may cause serious side effects, including:

Low blood cell counts. Low blood counts are common with LONSURF and can sometimes be severe and life-threatening. LONSURF can cause a decrease in your white blood cells, red blood cells, and platelets. Low white blood cells can make you more likely to get serious infections that could lead to death. Your healthcare provider may:

- lower your dose of LONSURF or stop LONSURF if you have low white blood cell or low platelet counts.

Tell your healthcare provider right away if you get any of the following signs and symptoms of infection during treatment with LONSURF:

- fever
- chills
- body aches

See **"What are the possible side effects of LONSURF?"** for more information about side effects.

What is LONSURF?

LONSURF is a prescription medicine used:

- alone or in combination with the medicine bevacizumab to treat adults with colorectal cancer:
  - that has spread to other parts of the body, **and**
  - who have been previously treated with certain chemotherapy medicines.
- alone to treat adults with a kind of stomach cancer called gastric cancer including adenocarcinoma of the gastroesophageal junction:
  - that has spread to other parts of the body, **and**
  - who have been previously treated with at least 2 types of treatment which included certain medicines.

It is not known if LONSURF is safe and effective in children.

Before you take LONSURF, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney or liver problems
- are pregnant or plan to become pregnant. LONSURF can harm your unborn baby.
  For females who can become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with LONSURF.
  - You should use effective birth control during treatment with LONSURF and for at least 6 months after your last dose of LONSURF. (Talk to healthcare provider about methods of birth control that can be used during this time)
  - Tell your healthcare provider right away if you become pregnant.

  For males:
  - You should use a condom during sex with female partners who are able to become pregnant during your treatment with LONSURF and for 3 months after your last dose of LONSURF. Tell your healthcare provider right away if your partner becomes pregnant while you are taking LONSURF.
- are breastfeeding or plan to breastfeed. It is not known if LONSURF passes into breast milk. Do not breastfeed during treatment with LONSURF and for 1 day after your last dose of LONSURF.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take LONSURF?

- Take LONSURF exactly as your healthcare provider tells you.
  LONSURF comes in two strengths. Your healthcare provider may prescribe both strengths for your prescribed dose.
- Take LONSURF 2 times a day with food.
- Swallow LONSURF tablets whole.
- Your caregiver should wear gloves when handling LONSURF tablets.
- If you vomit right after taking a dose, or miss a dose of LONSURF, do not take additional doses to make up for the vomited or missed dose. Call your healthcare provider for instructions about what to do for a missed dose.
- Wash your hands after handling the LONSURF tablets.

What are the possible side effects of LONSURF?

LONSURF may cause serious side effects, including:

- See **"What is the most important information I should know about LONSURF?"**

The most common side effects of LONSURF when used alone include:

- low blood counts
- tiredness and weakness
- nausea
- decreased appetite
- diarrhea
- vomiting
- stomach-area (abdominal) pain
- fever

The most common side effects of LONSURF when used in combination with bevacizumab include:

- low blood counts
- tiredness and weakness
- nausea
- certain abnormal liver function blood tests
- decreased salt (sodium) in your blood
- diarrhea
- stomach-area (abdominal) pain
- decreased appetite

Tell your healthcare provider if you have nausea, vomiting, or diarrhea that is severe or that does not go away.

These are not all of the possible side effects of LONSURF. For more information, ask your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LONSURF?

- Store LONSURF at room temperature between 68°F and 77°F (20°C and 25°C).
- If you store LONSURF outside of the original bottle, throw away (dispose of) any unused LONSURF tablets after 30 days.
- Talk to your healthcare provider about how to safely dispose of LONSURF.

Keep LONSURF and all medicines out of the reach of children.

General information about the safe and effective use of LONSURF

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LONSURF for a condition for which it was not prescribed. Do not give LONSURF to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about LONSURF that is written for health professionals.

What are the ingredients in LONSURF?

Active ingredients: trifluridine and tipiracil hydrochloride

Other ingredients: lactose monohydrate, pregelatinized starch, stearic acid, hypromellose, polyethylene glycol, titanium dioxide, ferric oxide, and magnesium stearate

Imprinting ink: shellac, ferric oxide red, ferric oxide yellow, titanium dioxide, FD&C Blue No. 2 Aluminum Lake, carnauba wax, and talc.

Manufactured by: Taiho Pharmaceutical Co., Ltd., Japan
Manufactured for: Taiho Oncology, Inc., Princeton, NJ 08540 USA

For more information, go to www.Lonsurf.com or call 1-844-878-2446.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 8/2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s012

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Taiho Oncology, Inc.
NDA Multi-Disciplinary Review and Evaluation

Application Type	SE-1
Application Number(s)	sNDA 207981/0012
Priority or Standard	Priority
Submit Date(s)	February 13, 2023
Received Date(s)	February 13, 2023
PDUFA Goal Date	August 13, 2023
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	Refer to electronic stamp date
Established/Proper Name	Trifluridine and tipiracil (TAS102)
Trade Name	Lonsurf
Pharmacologic Class	Thymidine phosphorylase inhibitor
Applicant	Taiho Oncology, Inc
Dosage form	Tablet, film coated
Applicant proposed Dosing Regimen	35 mg/m^2, orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle in combination with bevacizumab
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with metastatic colorectal cancer as a single agent or in combination with bevacizumab who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy
Recommended Dosing Regimen	35 mg/m^2/dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle in combination with bevacizumab

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Reviewers of Multi-Disciplinary Review and Evaluation

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OSI	John Lee/Philip Kronstein

OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medication and Policy Planning
OSI=Office of Scientific Investigations

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
BID	twice daily
BLA	biologics license application
BOR	best overall response
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	common terminology criteria for adverse events
DCO	Data cutoff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Easter Cooperative Oncology Group
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	final analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
GHS	global health status
GT	group term

HR	hazard ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
iPSP	initial pediatric study plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSI-H	
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
ODAC	Oncologic Drugs Advisory Committee
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PRO	patient reported outcome
PT	preferred term
PFS	progression-free surviva
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QoL	quality of life
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SEER	surveillance epidemiology and end result
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TMB-H	tumor mutational burden-high

US	United States
VAS	Visual analogue scale

1 Executive Summary

1.1. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from an adequate and well controlled trial, SUNLIGHT (NCT04737187), to support claims of safety and effectiveness for the proposed indication. SUNLIGHT is a randomized, open-label, multicenter, global trial which evaluated FTD/TPI in combination with bevacizumab and FTD/TPI as a single agent in 492 adult patients with metastatic colorectal cancer (mCRC) who had received a maximum of two prior chemotherapy regimens for advanced CRC and had demonstrated progressive disease or intolerance to their last regimen. Patients were randomized to receive FTD/TPI 35 mg/m^2 administered orally twice daily on Day 1 to Day 5 and Day 8 to Day 12 with or without bevacizumab 5 mg/kg administered intravenously (IV) every 2 weeks (on Day 1 and Day 15) of each 28-day cycle until disease progression or unacceptable toxicity. The primary objective was to demonstrate the overall survival (OS) superiority of FTD/TPI and bevacizumab versus FTD/TPI. The key secondary objective was to demonstrate superior progression free survival (PFS) of FTD/TPI and bevacizumab versus FTD/TPI as a single agent.

The application contains substantial evidence that FTD/TPI administered at 35 mg/m^2 orally twice daily on Days 1 to 5 and Days 8 to 12 with bevacizumab 5 mg/kg IV every 2 weeks of each 28-day cycle in adults with previously treated mCRC is safe and effective. SUNLIGHT demonstrated a statistically significant and clinically meaningful improvement in OS in patients randomized to the FTD/TPI plus bevacizumab arm compared to those who were randomized to the FTD/TPI arm (estimated HR of 0.61 [95% CI: 0.49, 0.77]).

The safety profile of FTD/TPI has been well characterized in other trials. The safety profile of FTD/TPI administered in combination with bevacizumab is consistent with the safety profile observed when each component of the combination regimen is administered as a single agent. The review team finds that the magnitude of improvement in the observed OS in the SUNLIGHT trial represents a clinical benefit that outweighs the risk of AEs in the indicated patient population.

Therefore, the review team recommends granting traditional approval to FTD/TPI in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.2. Product Introduction

LONSURF is a combination of trifluridine (FTD), a nucleoside metabolic inhibitor, and tipiracil (TPI), a thymidine phosphorylase inhibitor. FTD/TPI initially received approval on September 22, 2015, for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Currently, FTD/TPI is also approved for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.

FTD/TPI is supplied as 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil tablets for oral use. The recommended dosage is 35 mg/m^2 administered orally twice daily with food on Day 1 through Day 5 and Day 8 through Day 12 of each 28-day cycle.

In this supplemental application, the Applicant is seeking approval of FTD/TPI in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Colorectal cancer (CRC) is estimated to be the fourth most common cancer diagnosed and the second most common cause of cancer death in the United States (US) in 2023, comprising 7.8% of all new cancer cases with an estimated 153,020 new cases of CRC and 52,550 CRC deaths (SEER 22). The 5-year relative survival rate for patients diagnosed with metastatic CRC is 15.6% and median survival has been observed to be between 2 to 3 years (SEER 22, Biller et al. 2021). However, patients with metastatic CRC who have progressed following standard treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy and targeted therapies such as an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy, the prognosis is poor with a survival of approximately 5 months observed in patients who received placebo in clinical trials of regorafenib or FTD/TPI in the third-line setting. Available treatment options are limited for patients with refractory CRC and include treatment with regorafenib or FTD/TPI. FTD/TPI was approved in 2015 based on data from the RECOURSE trial that demonstrated an improvement in overall survival (OS) in patients treated with FTD/TPI compared to placebo (HR=0.68, [95% CI 0.58, 0.81]). The median OS of patients treated with FTD/TPI was 7.1 months (95% CI: 6.5, 7.8) compared to 5.3 months (95% CI: 4.6, 6) in patients who received placebo (Lonsurf PI). Regorafenib was approved in 2012 based on data from the CORRECT trial that demonstrated an improvement in OS in patients receiving regorafenib compared to patients receiving placebo (HR 0.77, [95% CI: 0.64, 0.94]); median OS was 6.4 months with a HR 0.77 (95% CI: 0.64, 0.94) compared to 5 months (95% CI: 4.4, 5.8) in patients who received placebo (Stivarga PI).

The Applicant submitted data from the SUNLIGHT trial to support approval of FTD/TPI in combination with bevacizumab for the treatment of adult patients with metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. A favorable risk:benefit assessment has been established for FTD/TPI in combination with bevacizumab based on a demonstration of a statistically significant and clinically meaningful improvement in OS in patients randomized to the FTD/TPI plus bevacizumab arm compared to patients who were randomized to FTD/TPI (HR of 0.61 ([95% CI: 0.49, 0.77], 1-sided p-value <0.001). The OS benefit was supported by the analysis of progression-free survival (PFS) which demonstrated a statistically significant improvement in patients randomized to FTD/TPI plus bevacizumab compared to patients who were randomized to single agent FTD/TPI (HR of 0.44 ([95% CI: 0.36, 0.54], 1-sided p-value <0.001).

The data submitted to support the safety review of FTD/TPI plus bevacizumab is adequate to characterize the toxicity in patients with

chemotherapy-refractory, metastatic CRC. The safety profile observed in patients who received FTD/TPI plus bevacizumab is generally consistent with what has been observed in patients treated with single agent FTD/TPI and single agent bevacizumab.

Risk minimization strategies have been instituted via management guidelines included in the product labeling and Medication Guide. An analysis of AEs thought to be in patients treated with FTD/TPI identified myelosuppression. Myelosuppression was previously listed in the Warnings and Precautions section of the FTD/TPI label.

The review team recommends traditional approval of FTD/TPI in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Colorectal cancer accounts for 7.8% of all new cancer cases. • It is estimated that there will be 153,020 new cases of colorectal cancer and 52, 550 colorectal cancer deaths in 2023 (SEER 22). • The 5-year relative survival rate of metastatic colorectal cancer is 15.6%. • New cases of colorectal cancer are diagnosed at a higher rate in Black individuals compared to other racial groups, with the average rate of new colorectal cases observed to be 36 in Blacks, 34.3 in American Indian and Alaskan Natives, 32.9 in Whites, 24.3 in Asian and Pacific Islanders per 100,000, and at a rate of 28 per 100,000 in Hispanic/Latino individuals (U.S. Cancer Statistics Working Group 1999-2020).	Refractory colorectal cancer is a serious and life-threatening condition with a poor prognosis.
Current Treatment Options	• Standard of care therapy after treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens includes treatment with either regorafenib or FTD/TPI, both of which were approved based on improvements in overall survival (OS) but demonstrated an ORR of	Standard of care options for the treatment of patients with metastatic CRC who have progressed on fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	1.6% (Mayer R, 2015). • In the CORRECT trial, regorafenib demonstrated an improvement in OS in patients receiving regorafenib compared to patients receiving placebo (HR 0.77, [95% CI: 0.64, 0.94]). • In the RECOURSE trial, FTD/TPI demonstrated an improvement in OS in patients treated with FTD/TPI compared to placebo (HR=0.68, [95% CI 0.58, 0.81]).	targeted therapies such as an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy is limited and have demonstrated only modest improvement in outcomes.
Benefit	• In the SUNLIGHT trial, FTD/TPI in combination with bevacizumab demonstrated a statistically significant and clinically meaningful improvement in OS compared to FTD/TPI as a single agent (HR of 0.61 [95% CI: 0.49, 0.77]). • The trial demonstrated a statistically significant improvement in investigator assessed progression-free survival (PFS) for the FTD/TPI and bevacizumab arm compared to the FTD/TPI arm (HR of 0.44 [95% CI: 0.36, 0.54]).	The study met its primary objective with FTD/TPI plus bevacizumab demonstrating superiority in OS over FTD/TPI as a single agent. A statistically significant effect on OS that is also clinically meaningful can be used to support approval of drugs intended for the treatment of mCRC.
Risk and Risk Management	• The safety analysis population included 246 patients treated with FTD/TPI plus bevacizumab and 246 patients treated with FTD/TPI as a single agent in the SUNLIGHT trial. • The primary risks of FTD/TPI plus bevacizumab include myelosuppression, gastrointestinal upset, and hypertension. • The most common adverse reactions or laboratory abnormalities (≥20% in incidence) in patients treated with FTD/TPI in combination with bevacizumab were neutropenia, anemia, thrombocytopenia, fatigue, nausea, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, decreased sodium, diarrhea, abdominal pain, and decreased appetite. • Serious adverse reactions occurred in 25% of patients. Fatal adverse reactions occurred in 1.2% of patients who received FTD/TPI plus	The observed safety profile of FTD/TPI in combination with bevacizumab is consistent with the safety profile observed with FTD/TPI and bevacizumab when each is administered as a single agent. This safety profile is acceptable when assessed in the context of a life-threatening disease. No new safety concerns were identified during the review. The observed adverse reactions were manageable with dose modifications. The risk of severe or serious myelosuppression is adequately addressed in the Warnings and Precautions and Dosage Modifications sections

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	bevacizumab, including rectal fistula (0.4%), bowel perforation (0.4%) and atrial fibrillation (0.4%).	of the product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
x	**The patient experience data that were submitted as part of the application include:**			
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	8.1.2, 8.2.6
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

X

Jamie Brewer, MD
Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and second in females worldwide (1). Approximately 153,020 new cases of CRC and 52,550 deaths are expected in the United States (US) in 2023 (2). It is now the second most common cause of cancer deaths in the US (2).

The rate of new cases of CRC was 37.7 per 100,000 males and females per year based on 2015–2019 cases, age-adjusted (3). CRC is more common in males than females and among those of African American descent (Table 1- Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colorectal CancerTable 1).

Table 1- Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer

	MALES	FEMALES
ALL RACES	42.1	32.0
Non-Hispanic white	42.3	32.5
Non-Hispanic black	50.4	37.2
Non-Hispanic Asian/pacific islander	35.3	25
Non-Hispanic American/Indian Alaska Native	52.3	45.1
Hispanic	39.6	32.5

Source – SEER 22 (2016-2020) seer.cancer.gov

Data from SEER database suggests that the incidence of CRC has been rising in individuals who are under the age of 50 years while decreasing in individuals in older age groups (4). The proportion of new CRC cases among adults under the age of 55 years increased from 11 to 20 percent between 1995 and 2019 (2). While it is known that genetic and environmental factors contribute toward risk for CRC, the reasons for the rise in incidence in the younger population is not fully understood.

The median age at diagnosis for CRC in the US is 66 years (4). Age distribution for diagnosis of colorectal cancer is presented in Table 2.

Table 2- Percent of New Cases by Age Group: Colorectal Cancer

Age group	Percentage of new cases (%)
<20	0.3
20-34	2
35-44	4.9
45-54	15
55-64	23
65-74	26
75-84	19
>84	10

Source - seer.cancer.gov

The death rate from CRC was 13.1 per 100,000 males and females per year based on 2016–2020 deaths, age-adjusted (3). Death rare by race/ethnicity is presented below in Table 3.

Table 3 - Death Rate per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer

	MALES	FEMALES
ALL RACES	15.7	11
Non-Hispanic white	15.5	11.1
Non-Hispanic black	22.3	14.3
Non-Hispanic Asian/pacific islander	10.9	7.7
Non-Hispanic American/Indian Alaska Native	20.8	14.3
Hispanic	13.5	8.5

Source - seer.cancer.gov

At diagnosis, 22% of patients have metastatic disease and 36% of patients have regional spread. Current median survival of metastatic CRC (mCRC) in the US is approximately 33 months but can vary based on certain factors including tumor specific factors (e.g., KRAS or BRAF mutations). (5) Median survival for patients in the 3rd line setting is approximately 5 months (Lonsurf USPI, Stivarga USPI).

2.2. Analysis of Current Treatment Options

The current standard of care for front-line treatment of patients with mCRC includes chemotherapy with a fluoropyrimidine-based regimen in combination with oxaliplatin or irinotecan and a biologic agent based on the biomarker profile and sidedness of the tumor. Patients with left-sided tumors that are KRAS wild type can receive systemic chemotherapy in combination with an anti-EGFR antibody as front-line therapy. Bevacizumab, an inhibitor of VEGF, is approved for use in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy in front-line as well as those whose disease have progressed on a first-line bevacizumab-containing regimen. In patients with microsatellite-instability high (MSI-H) mCRC (4-5% of the metastatic population) pembrolizumab is approved as front-line therapy.

Ziv-Aflibercept, a soluble receptor for VEGF is approved for use in combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen. Ramucirumab is a VEGF receptor 2 antagonist approved for use in combination with FOLFIRI for the treatment of patients with mCRC whose disease has progressed on a first-line bevacizumab-, oxaliplatin- and fluoropyrimidine-containing regimen.

Approved therapies in the 3rd line setting include regorafenib and FTD/TPI, which have demonstrated modest effects on OS (Table 4).

Table 4– FDA Approved-Third Line Therapy for mCRC

Treatment	Pivotal Trial Treatment Arms (n)	Median OS (months)	Median PFS (months)	ORR (%)
Regorafenib (Stivarga®)[a]	Regorafenib=500; Placebo =253	6.4 vs 5.0; HR=0.77 (95% CI: 0.64–0.94); p=0.0052	1.9 vs 1.7; HR=0.49 (95% CI: 0.42–0.58); p=0.0001	1.0 vs 0.4
Trifluridine and tipiracil (Lonsurf®)[b]	Trifluridine and tipiracil=534; Placebo=266	7.1 vs 5.3; HR=0.68 (95% CI: 0.58–0.81); p<0.001	2.0 vs 1.7; HR=0.48 (95% CI: 0.41–0.57); p=0.001	1.6 vs 0.4

Source- a= Grothery A etal, Lancet. 2013 Jan 26;381(9863):303-12. b= Mayer RJ et al, N Engl J Med 2015; 372:1909-1919

Immune checkpoint inhibitors (pembrolizumab, nivolumab in combination with ipilimumab) are also approved for treatment after prior systemic therapy in patients with MSI-H mCRC and patients with tumor burden mutation-high (TMB-H) mCRC; however, most of these patients would have typically received immunotherapy as first-line therapy. The combination of encorafenib (a BRAF inhibitor) and cetuximab is approved for patients

with BRAF-mutated mCRC (4-5% of the metastatic population) who have received one or two prior regimens (6).

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FTD/TPI was initially approved in 2015 for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

FTD/TPI was subsequently approved for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy in

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 5 summarizes the key regulatory interactions for the SUNLIGHT trial.

Table 5 - Key Regulatory Interactions, SUNLIGHT Trial

Date	Description
September 21, 2020	FDA issued final meeting minutes for a Type B meeting held on September 18, 2020, to discuss the clinical development plan to expand the indication of FTD/TPI to be used in combination with bevacizumab in patients with chemo-refractory mCRC. based on the results of study CL3-95005-007 (SUNLIGHT).
January 28, 2021	An IND amendment was submitted containing a new protocol for Study CL3-95005-007 - An Open-Label, Randomized, Phase III Study Comparing Trifluridine/Tipiracil in Combination with Bevacizumab to Trifluridine/Tipiracil Monotherapy in Patients with Refractory Metastatic Colorectal Cancer (SUNLIGHT).
March 12, 2021	FDA completed the review of the SUNLIGHT protocol submission and sent an advice and information request letter seeking clarification on the bevacizumab products that would be allowed on study and providing additional censoring rules for the primary analysis of PFS.
April 20, 2021	IND amendment was submitted to provide a formal response to the March 12, 2021, FDA advice and information request letter.
October 14, 2022	Initial Pediatric Study Plan (iPSP) was submitted detailing the plan to request a full waiver from the requirement for conducting

Date	Description
	pediatric studies for the treatment of "colorectal cancer" on the basis that necessary studies are impossible or highly impractical.
December 29, 2022	FDA issued final meeting minutes for the Type B teleconference meeting held on December 21, 2022, to discuss the planned supplemental NDA submission for LONSURF in combination with bevacizumab in third-line mCRC.
January 6, 2023	Taiho submitted a post-meeting clarification to explain the discrepancy between the clinical data cutoff (DCO) and the survival DCO in response to discussion at the December 29, 2022, Type B meeting.
January 11, 2023	FDA completed review and issued comments to the initial iPSP.
January 13, 2023	An IND amendment containing the Agreed iPSP was submitted with no new revisions.

A diversity plan was not submitted for this development program.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to audit the overall trial conduct for the SUNLIGHT trial. Three clinical sites, Site 1005 (Spain, Elena Elez), Site 206 (Brazil, Felipe José Cruz) and Site 1007 (Spain, Gemma Soler), were selected for audit. No significant discrepancies between the source documents and data line listings were observed. Study files and subject case records were well maintained. The inspection confirmed adequate compliance with Good Clinical Practice (GCP) principles and regulations. Unreported protocol deviations were not discovered. The major efficacy endpoint and adverse event (AE) data reported in the application were audited in detail and were determined to be verifiable against the source data recorded at the clinical sites. Based on the inspection findings, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this New Drug Application (NDA).

4.2. Product Quality

The submission did not contain new product information.

4.3. Clinical Microbiology

The submission did not contain new clinical microbiology information.

4.4. Devices and Companion Diagnostic Issues

The submission did not require a device or companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

No new nonclinical data are being submitted in the current application.

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6 Clinical Pharmacology

No new clinical pharmacology data are being submitted in the current application.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6 presents details of the SUNLIGHT study that support the safety and efficacy in the proposed indication, as well as additional studies to support the review of safety.

Table 6 6 – Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ FU	No. of patients enrolled	Study Population	Sites
Controlled Studies to Support Efficacy and Safety							
SUNLIGHT (NCT04737187)	Phase 3, multinational, open label, controlled two-arm, randomized (1:1) study	FTD/TPI: 35 mg/m^2 orally (PO) twice daily (BID) on days 1-5 and 8-12 q28 days Bevacizumab: 5 mg/kg IV on days 1 and 15 of a 4-week cycle with FTD/TPI	**Primary endpoint:** OS **Secondary endpoint:** Investigator assessed PFS	Until disease progression or unacceptable toxicity	492 **FTD/TPI plus bevacizumab**: 246 **FTD/TPI**: 246	mCRC who have already received a maximum of 2 prior regimens	99 sites, 13 countries (US, EU, Brazil, Russia, Ukraine)
Other studies pertinent to the review of efficacy or safety							

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ FU	No. of patients enrolled	Study Population	Sites
RECOURSE	Phase 3, multinational, randomized, double-blind study (2:1 randomization)	FTD/TPI: 35 mg/m^2 PO BID on days 1-5, and 8-12 q28 days Placebo	OS	until disease progression or unacceptable toxicity	800	mCRC, who had received prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy when appropriate	Japan, US, Europe, Australia
TAGS	Phase 3, randomized, double-blinded study	FTD/TPI: 35 mg/m2 PO BID on days 1-5, and 8-12 q 28 days Placebo	OS	Until disease progression or unacceptable toxicity	507	Metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan,	Japan, US, Europe, Australia

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ FU	No. of patients enrolled	Study Population	Sites
						and if appropriate, HER2/neu-targeted therapy	
SOLSTICE	Phase 3 randomized, open-label, study (1:1 randomization)	FTD/TPI: 35 mg/m^2 PO BID days 1-5, and 8-12 q28 days plus Bevacizumab: 5 mg/kg IV given on days 1 and 15 of a 4-week cycle with FTD/TPI Capecitabine: 1250 or 1000 mg/m^2 PO BID days 1-4 q3 weeks plus Bevacizumab: 5 mg/m^2 IV days 1 and15 of a 4-week cycle	PFS- INV assessed	Until disease progression or unacceptable toxicity	854	mCRC patients who are not eligible for intensive first line therapy due to clinical condition (elderly, comorbidities, ECOG PS) or nonclinical condition (low tumor burden, patient's preference, other)	25 countries-global study Europe, South America.

7.2. Review Strategy

The clinical and statistical reviewers reviewed the following:

1. Published literature on the epidemiology, biology, and treatment of mCRC.
2. Relevant meeting minutes from IND 057674.
3. The SUNLIGHT trial study report, protocol, protocol amendments, Independent Review Committee Charter, statistical analysis plan and amendments, select case report forms, and patient narratives.
4. Review and analysis of relevant efficacy and safety datasets and SAS programming algorithms to confirm efficacy measures and evaluate the risk:benefit profile.
5. The Applicant's Summary of Clinical Safety and the Integrated Summary of Safety which included tabular data for comparison with RECOURSE and TAGS trials for single agent FTD/TPI. Comparative safety results from the SOLSTICE trial were shared for FTD/TPI plus bevacizumab.
6. Consultation reports from OSI.
7. The Applicant's responses to FDA requests for additional information.
8. The regulatory history of other drugs approved for mCRC.
9. Review and evaluation of proposed labeling.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CL3-95005-007 (SUNLIGHT)

Trial Design

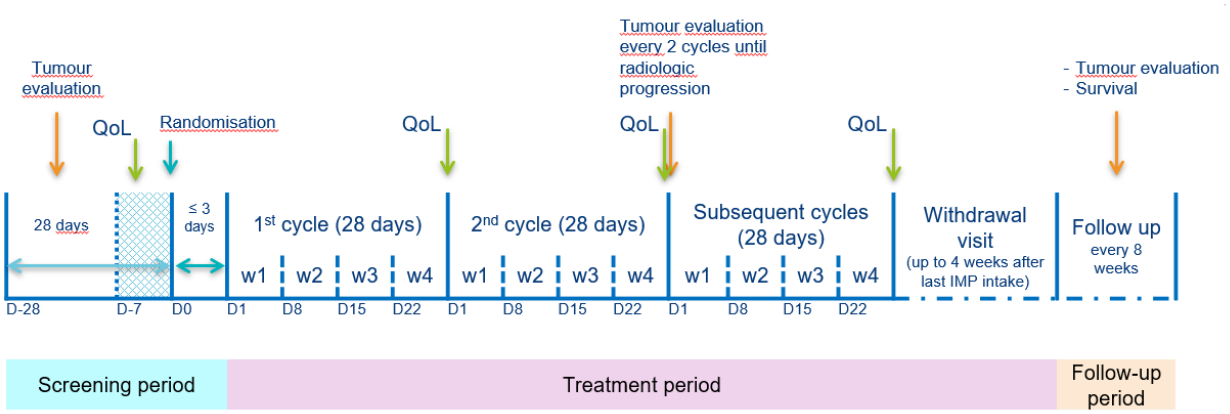
Trial CL3-95005-007 (SUNLIGHT) is a multinational, randomized, open-label, two-arm study evaluating the efficacy and safety of FTD/TPI plus bevacizumab in patients with refractory mCRC who have received a maximum of two prior chemotherapy regimens for advanced CRC and had progressive disease or intolerance to their last regimen.

Patients were randomized (1:1) to one of the two treatment arms: FTD/TPI plus bevacizumab (experimental arm) or FTD/TPI monotherapy (control arm). Randomization was stratified by geographic region (North America, European Union, Rest of the World), time since first metastasis diagnosis (<18 months, ≥18 months) and RAS status (wild-type, mutant).

The study (figure below) consisted of the following periods:

- Screening period and inclusion: The eligibility of the patient to be included and randomized in the study was checked.
    - Screening visit (up to 28 days prior to randomization) was to obtain informed consent.
- Treatment period: Randomized patients received the first dose of study treatments (C1D1) within 3 days after randomization and continued until they met a discontinuation criterion
    - Tumor assessments of the chest, abdomen and pelvis (and other areas if clinically indicated) via CT or MRI were performed according to RECIST version 1.1 every 2 cycles (i.e., 8 weeks) until radiographic progression or the end of study. The same method of assessment and the same technique had to be used for all evaluations.
    - The withdrawal visit occurred within 4 weeks following the date of study treatment withdrawal and before the start of a new anticancer therapy.
- Post-withdrawal follow-up period: After the withdrawal visit, the patient was Followed for:
    - tumor assessment every 8 weeks until radiologic progression regardless of initiation of a new anticancer therapy (unless patient had discontinued study treatment for radiologic disease progression or withdrawal of consent).
    - survival status every 8 weeks until death or the end of the study (whichever first occurred).

Figure 1. Study design, SUNLIGHT Trial



Source: Study Protocol Figure 4.1.1

The end of study was anticipated to occur 19 months after the first study treatment of the last patient randomized and was defined as the date of the last follow-up of the last patient or the date of the last contact attempt if the last patient was declared lost to follow-up. Upon study completion, patients still being treated were to be offered the option to continue treatment outside the study.

Key Inclusion Criteria

- Male or female patients aged ≥18 years at the time of informed consent signature.
- Had histologically confirmed unresectable adenocarcinoma of the colon or rectum.
- RAS status had been previously determined (mutant or wild-type) based on local assessment of tumor biopsy.
- Had received a maximum of two prior chemotherapy regimens for the treatment of advanced CRC and had demonstrated progressive disease or intolerance to their last regimen:
    - Prior treatment regimens for the treatment of advanced CRC had included a fluoropyrimidine, irinotecan, oxaliplatin, a VEGF inhibitor and/or an EGFR inhibitor for RAS wild type patients.
    - Adjuvant/neoadjuvant chemotherapy could count as one prior regimen of chemotherapy for advanced CRC if the patient had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy.
- Had measurable or non-measurable disease as defined by RECIST version 1.1.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1.
- Adequate organ function (as defined in the protocol).

Key Exclusion Criteria

- More than 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer.
- Has previously received FTD/TPI.

- Deep arterial thromboembolic events including cerebrovascular accident or myocardial infarction within the last 6 months prior to randomization.
- Deep venous thromboembolic event within 4 weeks prior to randomization.
- Known coagulopathy that increases risk of bleeding, bleeding diatheses. Any other hemorrhage/bleeding event CTCAE Grade ≥3 within 4 weeks prior to randomization.
- Drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior to randomization.
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose (≤20 mg/day prednisone equivalent))

Study Endpoints

The primary endpoint of the study was OS, defined as the time between the date of randomization and the date of death due to any cause. For patients without documentation of death, OS was censored at the last contact date the patient was known to be alive or the survival cutoff date, whichever was earlier.

The key secondary endpoint was progression free survival (PFS) based on Investigator assessment according to RECIST version 1.1. PFS was defined as the time between the date of randomization and the date of radiologic tumor progression or death from any cause. For patients without documentation of death or radiological progression, PFS was censored at the date of last evaluable assessment or the survival cutoff date, whichever was earlier. Secondary endpoints also included overall response rate (ORR) and disease control rate (DCR) based on Investigator assessment per RECIST version 1.1. ORR was defined as the proportion of patients with objective evidence of complete response (CR) or partial response (PR). Other secondary objectives were to compare the safety and tolerance, and the impact on quality of life (QoL) of FTD/TPI plus bevacizumab to FTD/TPI monotherapy in patients with refractory mCRC.

Statistical Analysis Plan (SAP)

The original SAP was finalized on June 11, 2020. The DCO date for clinical data was July 5, 2022. The DCO date for survival data was July 19, 2022. No interim analysis for efficacy was planned in the study. The primary efficacy analysis was based on the DCO date for OS. Despite the difference in DCO, response data that was collected between the dates for the clinical data DCO and the survival data DCO did not change the results with respect to best overall response (BOR) and ORR. Specifically, overall response changed for only 4 patients (all changed from SD to PD) during the period between the two DCO dates (July 5 and 19, 2022). Duration of response (DOR) was not prespecified as an endpoint and therefore the data were not provided in the submission.

The sample size was calculated based on the primary endpoint of OS. A total of 331 OS events were required for the primary analysis to detect a hazard ratio (HR) of 0.70 with 90% power at a 1-sided 2.5% level of significance. A HR of 0.70 translates into a 3 month increase of the median OS in the experimental arm compared to the control arm (10.1 vs 7.1 months). A total of 490

patients were planned to observe 331 OS events, assuming an enrollment period of 12 months and a dropout rate of 5%.

Efficacy analyses and descriptive statistics for patient disposition and baseline characteristics were based on the Full analysis set (FAS), defined as the intention-to-treat (ITT) population.

For the time-to-event endpoints (OS and PFS), survival distribution and probabilities at specific timepoints were estimated using Kaplan-Meier method, with the corresponding 95% confidence interval (CI) constructed based on a log-log transformation using the method of Kalbfleisch and Prentice. Median survival time and its 95% CI were obtained based on a linear transformation for the survival function using the method of Brookmeyer and Crowley. The treatment difference was compared between the two treatment arms using a stratified log-rank test at a 1-sided 2.5% level of significance with Interactive Web response System (IWRS)-based stratification factors. The HR and its 95% CI were estimated with a stratified proportional hazards model using IWRS-based stratification factors.

Survival data collected after treatment discontinuation or new anticancer therapy were used for the primary efficacy analysis, which is aligned with the treatment policy strategy. Treatment crossover was also one of the predefined intercurrent events; however, no treatment crossover occurred during the study.

Three sensitivity analyses for PFS were prespecified to explore the impact of stratification, new anticancer therapy, and missing data. The first sensitivity analysis used unstratified log-rank test and unstratified proportional hazards model. The second analysis treated new anticancer therapy and clinical progression as *progressed*. The third analysis, recommended by FDA, treated new anticancer therapy and more than one missing assessment before death/progressive disease (PD) as *censored*, at the date of last evaluable assessment before or at the date of new anticancer therapy or at the latest evaluable assessment prior to the missing assessments.

To control the overall Type I error rate, OS and PFS were tested using a hierarchical testing strategy, where PFS was tested only if OS was statistically significant.

For tumor response, ORR and its 95% CI were estimated using Clopper-Pearson exact method.

SAP Amendment

The original SAP was amended once (Version 2.0, dated 02 Aug 2022). Key modifications are provided below:

- updated the definitions of treatment period and after treatment period,
- updated subgroup categories,
- added data handling according to a survival cutoff date, and
- added a sensitivity analysis for PFS.

Protocol Amendments

The original study protocol (dated June 10, 2020) was amended three times. The first two protocol amendments (Version 1.1 dated October 12, 2020, Version 1.2 dated November 5, 2020) were modified for European countries. The third amendment, Protocol Version 2.0, was finalized on December 30, 2020, with only minor modifications to the statistical parts of the protocol. The local amendment issued on December 30, 2020, for France specified that all patients in France should have received an anti-VEGF monoclonal antibody before entry in the study.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant reported that the study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in 2013, as revised in Fortaleza, 2013 with the GCP and according to applicable regulatory requirements.

Financial Disclosure

The Applicant provided financial disclosure information for the SUNLIGHT trial. There were a total of 719 investigators and sub-investigators, and all investigators certified that they did not have any financial interest or arrangements with the Applicant.

The Applicant certified that 1) the company has not entered any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity in the Sponsor; and 3) no listed investigator was the recipient of significant payments of other sorts.

Data Quality and Integrity

There were no major issues during the conduct of this study that had impacted the data quality or data integrity.

Patient Disposition

A total of 659 patients were screened and consented for the SUNLIGHT trial. A total of 167 patients (25%) of those screened were not enrolled either due to not meeting eligibility criteria (24%) or withdrawal of consent (1.1%).

A total of 492 patients were randomized 1:1 to the FTD/TPI monotherapy arm (n=246) and FTD/TPI plus bevacizumab arm (n=246). All of the 492 patients received the treatment assigned at randomization. As of the clinical cutoff date of July 5, 2022, 36 (7%) patients were still on treatment (13% in the FTD/TPI plus bevacizumab arm, 1.6% in the FTD/TPI monotherapy arm).

The most common reason for treatment discontinuation in both arms was clinical and/or radiological disease progression which occurred more in the FTD/TPI monotherapy arm as compared to FTD/TPI plus bevacizumab arm (89% vs 78%). AEs leading to treatment discontinuation was same in both arms (7% each). A total of 3.2% and 2.0% of patients withdrew consent in FTD/TPI monotherapy and FTD/TPI plus bevacizumab arm respectively.

Table 7- Patient Disposition, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	**FTD/TPI plus Bev N=246 n(%)**
Continuing treatment	4 (2)	32 (13)
Withdrawn from treatment	242 (98)	214 (87)
Disease progression	218 (89)	191 (78)
Adverse Event	16 (7)	16 (7)
Non-medical reason	8 (3)	5 (2)

Source: ADSL dataset

Reviewer's comment- Patients in the FTD/TPI plus bevacizumab arm stayed on treatment longer than those on FTD/TPI monotherapy arm due to longer time to disease progression. The rate of AEs leading to treatment discontinuation was not higher in the combination arm of FTD/TPI plus bevacizumab as compared to FTD/TPI monotherapy arm.

Protocol Violations/Deviations

A total of 51 patients had 57 important protocol deviation before or at study inclusion. These protocol deviations were balanced in the two arms (FTD/TPI monotherapy arm - 11%; FTD/TPI plus bevacizumab arm - 10%). In the overall study population, the most common reasons included patients who had received anticancer therapy within four weeks prior to randomization (13 patients, 2.6%) and those who received more than two prior chemotherapies for treatment for mCRC (12 patients, 2.4%). A local protocol amendment was made for study sites enrolling in France which mandated all patients to have received prior anti-VEGF therapy (bevacizumab or ramucirumab), however 4 out of 28 French patients received ziv-afilbercept instead. No important protocol deviation was reported for these four patients as the treatment was considered acceptable based on study criteria. A subset of important protocol deviations in the FAS population are listed below in **Table 7 8**. Of note, a sensitivity analysis was performed for the primary efficacy analysis that excluded patients in this predefined subset.

Table 7 8- Important Protocol Deviations in the FAS Population, SUNLIGHT Trial

Protocol deviations	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)	All N=492 n(%)
ALL	16 (7)	14 (6)	30 (6)
Selection/inclusion criteria not fulfilled	16 (7)	14 (6)	30 (6)
Patient has not demonstrated progressive disease or intolerance to the last regimen.	2 (0.8)	3 (1.2)	5 (1.0)
Patient have received more than 2 prior chemotherapies regimens for the treatment of advanced colorectal cancer.	6 (2.4)	6 (2.4)	12 (2.4)
Patient received anticancer therapies within 4 weeks prior to randomization.	8 (3.3)	5 (2.0)	13 (2.6)

Source : ADSL dataset

There was a total of 87 important protocol deviations which occurred in 49 patients during the study. While the number of patients with these protocol deviations was higher in the FTD/TPI plus bevacizumab arm compared to FTD/TPI monotherapy arm (14% vs 6%), the majority (protocol deviations in 33 out 47 patients) of these were related to timing of blood sample collection. There were 3 cases in which the calculated dose of bevacizumab was not accurate.

A total of 12 (4.9%) patients in the FTD/TPI plus bevacizumab arm and 4 (1.6%) patients in the FTD/TPI monotherapy arm needed changes or accommodation due to COVID-19 pandemic. The majority of these patients in the FTD/TPI plus bevacizumab arm were related to timing for lab sampling required prior to doing of bevacizumab.

Reviewer's comment- Overall the protocol deviations were mostly related to timing of sampling, and it is unlikely that the protocol deviations had an impact on the study results. The sensitivity analysis of OS excluding patients in the predefined subset of important protocol deviations was consistent with the primary analysis. The estimated HR was 0.59 (95% CI: 0.47, 0.74). Median OS was 10.8 months (95% CI: 9.6, 12.1) in the FTD/TPI plus bevacizumab arm vs 7.2 months (95% CI: 6.3, 8.5) in the FTD/TPI monotherapy arm.

Demographic and Other Characteristics

Demographics and baseline characteristics of patients enrolled on the SUNLIGHT trial are shown in Table 9 and Table 9.

Table 9- Patient Demographics, SUNLIGHT Trial

	FTD/TPI N=246 n (%)	FTD/TPI plus Bev N=246 n(%)
Sex		

	FTD/TPI N=246 n (%)	FTD/TPI plus Bev N=246 n(%)
Male	134 (54)	122 (50)
Female	112 (46)	124 (50)
Age (years)		
Median (Min - Max)	64 (24 - 90)	62 (20 - 84)
Age Group		
18 - 64 Years	129 (52)	146 (59)
≥65 - <75 Years	83 (34)	76 (31)
≥75 Years	34 (14)	24 (10)
Race		
White	220 (89)	215 (87)
Unknown	17 (7)	18 (7)
Other	5 (2)	8 (3.3)
Black/African American	3 (1.2)	4 (1.6)
Asian	1 (0.4)	0 (0)
American Indian/ Alaska Native	0 (0)	1 (0.4)
Country		
Spain	58 (24)	57 (23)
Russia	42 (17)	35 (14)
Brazil	30 (12)	33 (13)
Hungary	23 (9)	24 (10)
Poland	21 (9)	13 (5)
Italy	19 (8)	20 (8)
France	13 (5)	15 (6)
Denmark	10 (4.1)	10 (4.1)
Ukraine	9 (3.7)	12 (4.9)
USA	8 (3.3)	8 (3.3)
Belgium	5 (2.0)	2 (0.8)
Austria	5 (2.0)	10 (4.1)
Germany	3 (1.2)	7 (2.8)

Source: ADSL dataset

Table 10- Baseline Characteristics of Patients, SUNLIGHT Trial

	FTD/TPI N=246	**FTD/TPI plus Bev N=246**
Primary Site		
Colon	181 (73.6)	180 (73)
Rectum	65 (26)	66 (27)
Primary Tumor Localization		
Right	77 (31)	62 (25)
Left	169 (69)	184 (75)
Disease Duration (years)		
≤1	28 (11)	24 (10)
>1– 2	92 (37)	101 (41)
>2 – 4	83 (33)	94 (38)
>4	43 (18)	27 (11)
Time from First Metastasis Diagnosis to Randomization (months)		
<18	105 (43)	104 (42)
≥18	141 (57)	142 (58)
Site of metastases		
Liver	188 (76)	194(789)
Lung	154 (63)	157 (64)
Lymph node	101 (41)	95 (39)
Bone	30 (12)	22 (9)
Brain	2 (0.4)	2 (0.8)
Skin	1 (0.2)	1 (0.4)
Peritoneal	60 (24)	60 (24)
Soft tissue	9 (3.6)	9 (3.6)
Other	38 (16)	31 (13)
Number of metastatic sites		
1 – 2	141 (57)	152 (62)
≥3	105 (43)	94 (38)
Evaluable tumor		
Measurable disease	215 (87)	222 (90)
Non measurable disease	31 (130)	24 (10)
RAS status	**N=168**	**N=169**
Mutant	170 (69)	171 (69.)
Wild	76 (31)	75 (30)
BRAF status		
Mutant	11 (7)	8 (4.7)
Wild	156 (93)	159 (94)
Unknown/Not Interpretable	1 (0.6)	2 (1.2)
MMR/MSI status	**N=156**	**N=154**
Microsatellite High /Mismatch Repair Deficient	8 (5)	13 (8)

	FTD/TPI N=246	FTD/TPI plus Bev N=246
Microsatellite-Stable/MSI Low /Mismatch Repair Proficient	145 (93)	139 (90)
Unknown/Not Interpretable	3 (1.9)	2 (1.3)

Source: ADSL

The baseline disease characteristics were well balanced between the two arms. A total of 69% of patients treated with FTD/TPI monotherapy and 70% of patients treated with FTD/TPI plus bevacizumab had RAS mutant CRC. BRAF status was tested in 168/246 (68%) in the FTD/TPI monotherapy arm and 169/246 (69%) in the FTD/TPI plus bevacizumab arm. Ninety-three percent of patients (156/169) in the FTD/TPI monotherapy arm and 94% (159/168) in the FTD/TPI plus bevacizumab arm had BRAF wild type tumors. MMR/MSI tumor status was known in 63% of patients in both arms, of which only 5% (n=8) in the FTD/TPI monotherapy arm and 8% (n=13) in the FTD/TPI plus bevacizumab arm were MSI-H/MMR-deficient.

Receipt of anti-cancer therapy prior to enrollment was analyzed (Table 11), also focusing on prior anti-VEGF therapy use in both arms.

Table 11- Prior Anti-Cancer Therapy, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)
Number of prior metastatic[1] drug regimens		
1	15 (6)	11 (4.5)
2	224 (91)	229 (93)
≥3	7 (2.9)	6 (2.4)
Previous metastatic[1] drug treatment		
Fluoropyrimidine	246 (100)	246 (100)
Irinotecan	245 (99.6)	246 (100)
Oxaliplatin	243 (98.8)	241 (98)
Anti-VEGF[2]	187 (76)	188 (76)
Previous metastatic anti-VEGF monoclonal anti-body	176 (72)	178 (72)
Anti-EGFR monoclonal anti-body in RAS wild-type patients[3]	66 (278)[4]	67 (27)[4]

[1]Defined for the previous drug treatment (a) given in palliative setting or (b) given in adjuvant or neoadjuvant setting and with a progression before or within 6 months after the drug treatment completion.
[2]For anti-VEGF and anti-EGFR monoclonal antibody treatments, only monoclonal antibody agents are considered. Regarding
prior anti-VEGF monoclonal antibodies, these include bevacizumab and ramucirumab
[3]number of RAS wild type patients was 76 in FTD/TPI arm and 75 in FTD/TPI plus Bev arm per IWRS

[4]Percentages based on number of patients for whom RAS status was wild type
Source: ADSL dataset

Receipt of prior therapy was balanced between the two arms. The majority of RAS wild-type patients received anti-EGFR therapy in both arms (93% in FTD/TPI monotherapy arm and 94% in FTD/TPI plus bevacizumab arm). The proportion of patients that received prior anti-VEGF therapy was also balanced between the two arms.

Table 12- Subsequent Anticancer Systemic Therapy Received by Patients, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	**FTD/TPI plus Bev N=246 n(%)**
Patients with at least one treatment	**113 (46)**	**108 (44)**
Fluorouracil	42 (17)	45 (18)
Oxaliplatin	40 (16)	37 (15)
Irinotecan	26 (11)	37 (15)
Regorafenib	47 (19)	36 (15)
Capecitabine	28 (11)	20 (8)
Bevacizumab	18 (7)	19 (8)

Source: ADSL and ADCM datasets

Receipt of subsequent cancer therapy was analyzed and was balanced between the two arms with 46% of patients in the FTD/TPI monotherapy arm and 44% of patients in the FTD/TPI plus bevacizumab arm receiving subsequent anti-cancer therapies.

Reviewer's comment: The baseline characteristics, including prior anti-VEGF therapy and subsequent therapies appear well balanced in the two arms. Tumor BRAF status and MSI/MMR status information was missing in a more than 30% of the patients; however, given that the proportion of patients with missing molecular information for BRAF and MSI/MMR status were balanced between the two arms, the missing information is unlikely to have affected the interpretation of the efficacy results. As the primary endpoint of the study was OS, it was important to analyze if the receipt of subsequent therapy was balanced between study arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was measured by the number of FTD/TPI tablets dispensed and returned by the patient. Tablets were counted by the investigator or a designated person from their

team and recorded in the e-CRF and therapeutic unit tracking form, or an equivalent document. If the patient did not bring back all blister packs dispensed at the previous visit, the investigator estimated the number of FTD/TPI tablets taken by the patient since the previous visit, by questioning him/her. In the event of a missed dose, the patient had to indicate the reason to the investigator.

Treatment compliance was assessed by the relative dose intensity (RDI) during the overall treatment duration. The RDI (%) per patient was defined as the ratio of the dose intensity to the planned starting dose intensity at inclusion. The mean ± SD (median) RDI for FTD/TPI was similar in the FTD/TPI plus bevacizumab arm and in the FTD/TPI monotherapy arm: 85.0 ± 13.2 (88%) vs 87 ± 14.2 (90%), respectively. In the FTD/TPI plus bevacizumab arm, the mean ± SD (median) RDI for bevacizumab was 86.9 ± 27.3 (88%).

Overall, the use of concomitant medication at inclusion was similar between the two arms (85% in the FTD/TPI monotherapy arm vs 84% in the FTD/TPI plus bevacizumab arm). A similar percentage of patients in both arms used analgesics (FTD/TPI monotherapy- 35% and FTD/TPI plus bevacizumab -34%). The frequency of use of concomitant drugs for treatment of hypertension and cardiovascular disorder was also similar between the two arms.

In addition, the type of antihypertensive drugs used were comparable between the FTD/TPI monotherapy arm and the FTD/TPI plus bevacizumab arm: renin angiotensin pathway agents (31% vs 33%), beta blockers (18% vs 17%), calcium channel blockers (13% vs 12%), diuretics (9% vs 11%), and others (1.2% v 2.4%). Use of drugs related to cardiovascular health included lipid modifying agents (10% vs 9%), antithrombotic (24% vs 23%), and others (2.8% vs 2.8%) were similar between the two arms.

During the treatment period, 29% of patients in the FTD/TPI plus bevacizumab arm and 20% in the FTD/TPI monotherapy arm received Granulocyte-Colony Stimulating Factor (G-CSF).

Reviewer's comment: Treatment compliance was not decreased in the treatment arm and use of concomitant medications including those that are used for treatment of conditions that may be associated with the known safety profile of the studied drugs (FTD/TPI and bevacizumab) was similar in the two study arms.

Use of G-CSF was increased in the FTD/TPI plus bevacizumab arm and was thought to be related to longer exposure to study treatment of patients on this arm. Neutropenia is a known AE event of FTD/TPI.

Efficacy Results – Primary Endpoint

The primary efficacy results are based on the preplanned 331 OS events in the FAS population (N=492) as of the survival DCO of July 19, 2022. No treatment crossover occurred during the study. The study demonstrated a statistically significant improvement in OS for the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm (Table 13). The estimated

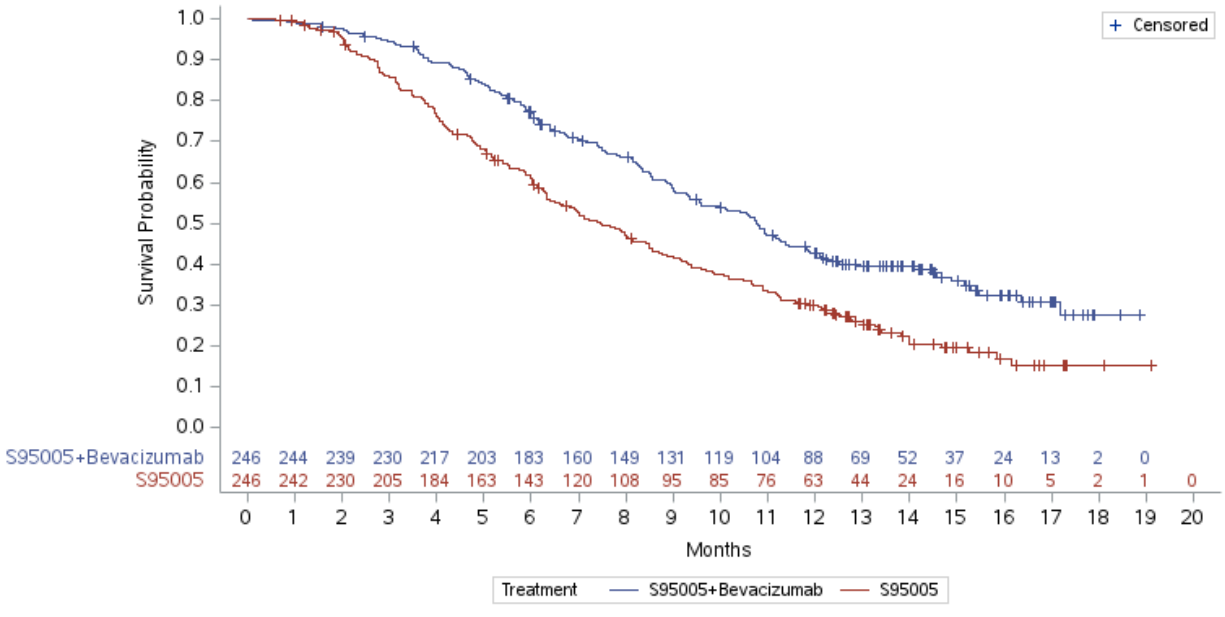
probability of surviving through 12 months was 43% (95% CI: 36, 49) in the FTD/TPI plus bevacizumab arm and 30% (95% CI: 24, 36) in the FTD/TPI monotherapy arm. The Kaplan-Meier curves started to separate at approximately 2 months and continued to separate, suggesting maintenance of treatment effect over time (Figure 2).

Table 13. Overall Survival, SUNLIGHT Trial (FAS)

	FTD/TPI plus Bev (N=246)	FTD/TPI (N=246)
Number of deaths, n (%)	148 (60)	183 (74)
Number of censored patients, n (%)	98 (40)	63 (26)
Median (95% CI), (months)[a]	10.8 (9.4, 11.8)	7.5 (6.3, 8.6)
P-value (1-sided)[b]	<0.001	
HR (95% CI)[c]	0.61 (0.49, 0.77)	

[a] *Based on Kaplan-Meier method*
[b] *Based on stratified log-rank test per IWRS (strata: region, time since first metastasis diagnosis, RAS status)*
[c] *Based on stratified proportional hazards model per IWRS (strata: region, time since first metastasis diagnosis, RAS status)*
Source: FDA reviewer

Figure 2. Kaplan-Meier Curves of Overall Survival, SUNLIGHT Trial (FAS)



Source: FDA reviewer

Efficacy Results – Secondary and other relevant endpoints

As of the DCO, the study demonstrated a statistically significant improvement in the key secondary endpoint of PFS assessed by investigator for the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm (Table 14). The Kaplan-Meier curves started to separate at approximately 2 months and continued to separate over time (Figure 3). The results of sensitivity analyses for PFS were consistent with that of the primary analysis.

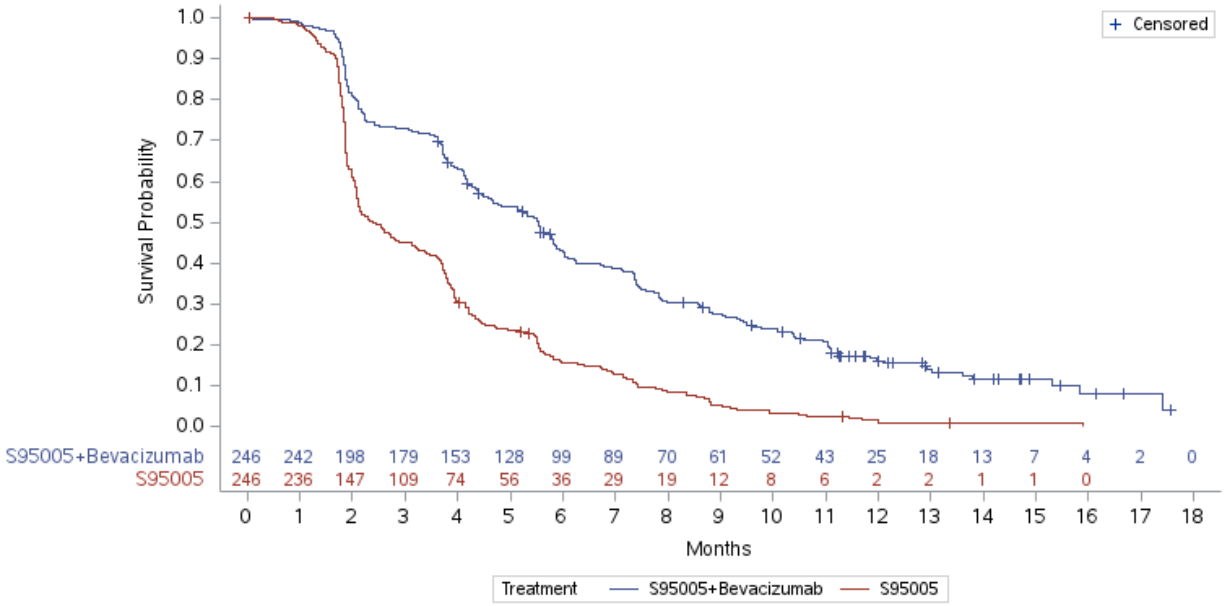
The descriptive statistics for ORR and BOR assessed by investigator are summarized in Table 13. Per SAP, the non-CR/non-PD category was only for patients with non-measurable disease and was included in the FAS population.

Table 14. Progression-Free Survival and Overall Response Rate, SUNLIGHT Trial (FAS)

	FTD/TPI plus Bev N=246	**FTD/TPI N=246**
PFS		
Number of events, n (%)	206 (84)	236 (96)
Progressive Disease	178 (72)	206 (84)
Death	28 (11)	30 (12)
Number of censored patients, n (%)	40 (16)	10 (4.1)
Median (95% CI), (months)[a]	5.6 (4.5, 5.9)	2.4 (2.1, 3.2)
P-value (1-sided)[b]	<0.001	
HR (95% CI)[c]	0.44 (0.36, 0.54)	
ORR (CR+PR), % (95% CI)[d]	6 (3.5, 10)	1.2 (0.3, 3.5)
Complete Response (CR)	0	1 (0.4)
Partial Response (PR)	15 (6)	2 (0.8)

[a] Based on Kaplan-Meier method
[b] Based on stratified log-rank test per IWRS (strata: region, time since first metastasis diagnosis, RAS status)
[c] Based on stratified proportional hazards model per IWRS (strata: region, time since first metastasis diagnosis, RAS status)
[d] Based on Clopper-Pearson method
Source: FDA reviewer

Figure 3. Kaplan-Meier Curves of Progression-Free Survival, SUNLIGHT Trial (FAS)

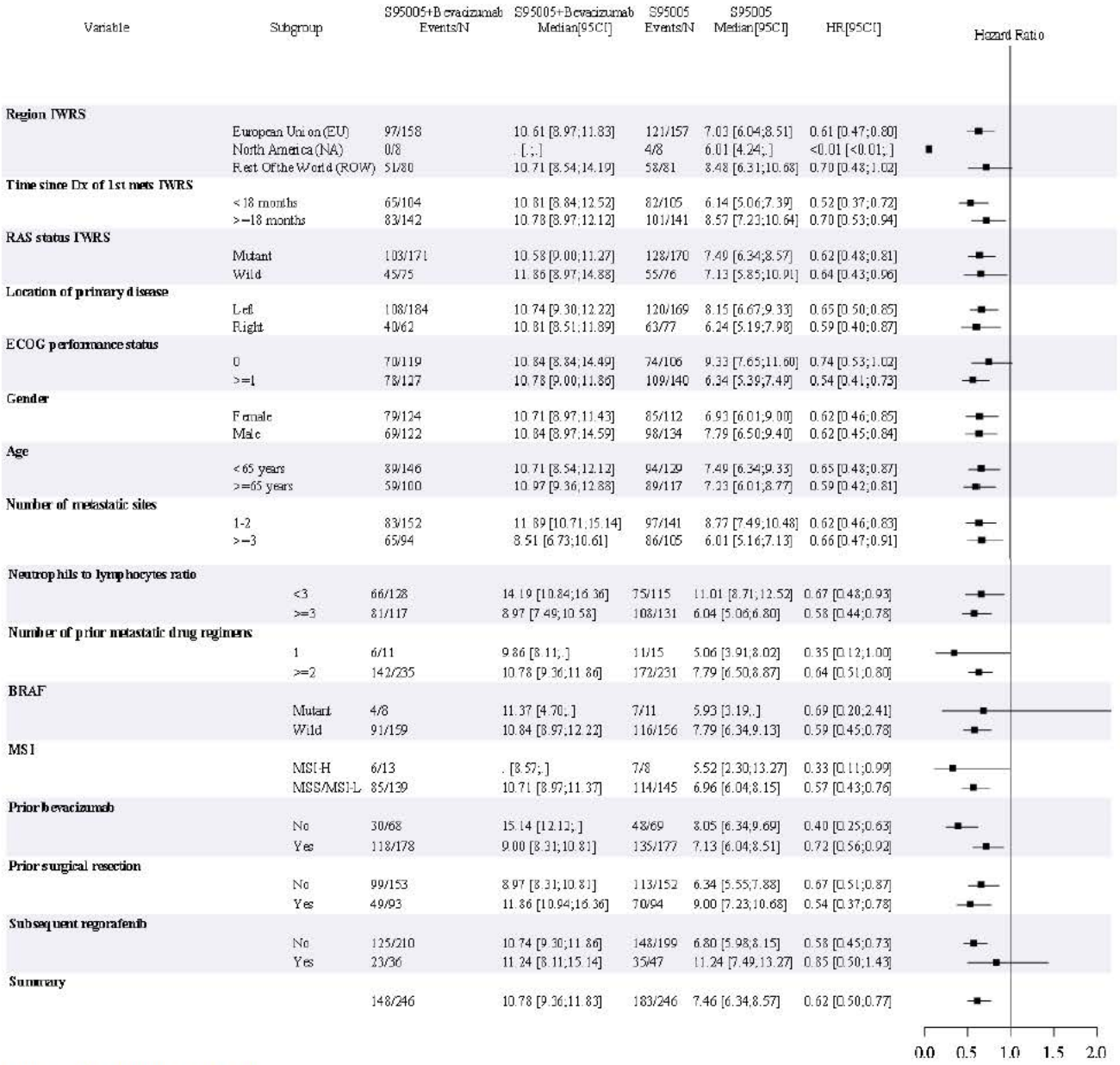


Source: FDA reviewer

Subgroup Analysis

The results of the prespecified subgroup analyses for OS are presented in Figure 4. HR and its 95% CI were estimated using an unstratified proportional hazards model. The treatment benefit in OS was generally consistent across the subgroups favoring the FTD/TPI plus bevacizumab arm. Small sample sizes in the subgroup categories, such as BRAF mutant, may result in unreliable estimates. FDA notes that all subgroup analyses conducted without formal testing are considered exploratory; therefore, no formal statistical inference can be drawn from these results, and results should be interpreted with caution.

Figure 4. Subgroup Analyses of Overall Survival, SUNLIGHT Trial (FAS)



Source: CSR Figure 11.1.3.1

Dose/Dose Response

Dose response relationships were evaluated in the review of the original NDA and were not repeated in the review of this application. Refer to the original application review for more information.

Durability of Response

A descriptive analysis of ORR and BOR was conducted (see Section 8.1.2: Efficacy Results –

Secondary and other relevant endpoints and Table 14), however duration of response was not prespecified as a study endpoint and therefore the data was not provided or assessed.

Persistence of Effect

See FDA analysis of PFS in Section 8.1.2: Efficacy Results – Secondary and other relevant endpoints.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Descriptive analysis for the quality of life (QoL) per EORTC QLQ-C30, conducted by the Applicant, showed that patients in the FAS population had similar QoL scores in the global health status (GHS), function, or symptom items across the treatment arms. No relevant mean change from baseline was observed in either arm. The percentage of patients with definitive GHS deterioration was lower in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm (49% vs 57%). The median time until definitive deterioration (TUDD) for GHS was greater in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm (8.5 vs 4.7 months). EQ-5D-5L utility score and visual analogue scale did not show relevant change from baseline in either arm.

For GHS, the completion rate decreased with each visit in both treatment arms. The compliance rate was ≥86% up to Cycle 11 and similar in the two treatments arms, except at Cycle 7 with a lower compliance rate in the FTD/TPI plus bevacizumab arm than in the FTD/TPI monotherapy arm (86% vs 100%).

FDA notes that although a formal testing of TUDD was prespecified in the SAP, this was not included in the testing hierarchy and Type I error was not appropriately adjusted for testing of multiple endpoints. Therefore, the analyses for PRO endpoints are considered exploratory and therefore are not independently verified by FDA.

Additional Analyses Conducted on the Individual Trial

No additional analyses have been conducted in the current submission.

8.1.3 Integrated Review of Effectiveness

The review of effectiveness for this application was based on the efficacy analyses conducted in the 492 patients in the FAS (ITT) population of the SUNLIGHT trial. The primary endpoint of OS met its prespecified significance with an estimated HR of 0.61 ([95% CI: 0.49, 0.77], 1-sided p-value <0.001). Median OS in the FTD/TPI plus bevacizumab arm was 10.8 months (95% CI: 9.4, 11.8) compared to 7.5 months (95% CI: 6.3, 8.6) in the FTD/TPI monotherapy arm. The OS benefit was consistent across most subgroups and supported by investigator assessed PFS and ORR. Particularly, median PFS in the FTD/TPI plus bevacizumab arm was 5.6 (95% CI: 4.5, 5.9)

compared to 2.4 months (95% CI: 2.1, 3.2) in the FTD/TPI monotherapy arm, demonstrating an improvement in PFS with an estimated HR of 0.44 ([95% CI: 0.36, 0.54], 1-sided p-value <0.001). The KM curves of both OS and PFS started to separate at approximately 2 months and separation was maintained throughout the study. Sensitivity analyses for PFS, including the FDA recommended analysis, were consistent with that of the primary PFS analysis. ORR was greater in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm (6% vs 1.2%). DOR was not prespecified as an endpoint and the data were not provided in the submission.

Taken together, these results provide adequate evidence of effectiveness of FTD/TPI in combination with bevacizumab in patients with refractory mCRC who have received a maximum of 2 prior chemotherapy regimens and had demonstrated progressive disease or intolerance to their last regimen.

8.1.4 Integrated Assessment of Effectiveness

The Applicant submitted an NDA supplement for FTD/TPI in combination with bevacizumab based on results of the SUNLIGHT trial. The trial enrolled 492 patients with advanced CRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. Patients were randomized 1:1 to FTD/TPI in combination with bevacizumab versus FTD/TPI monotherapy. The primary endpoint was OS and key secondary endpoint was investigator assessed PFS.

The study demonstrated a clinically meaningful and statistically significant improvement in OS for the FTD/TPI in combination with bevacizumab arm compared to the FTD/TPI monotherapy arm in the ITT population. The primary analysis results were consistent with the exploratory subgroup analyses and supported by PFS and ORR results per investigator assessment.

In summary, the results of the SUNLIGHT trial provide adequate evidence of effectiveness of FTD/TPI in combination with bevacizumab in patients with refractory mCRC who have received a maximum of two prior chemotherapy regimens and had demonstrated progressive disease or intolerance to their last regimen.

8.2 Review of Safety

8.2.1 Safety Review Approach

The safety analysis of FTD/TPI in combination with bevacizumab was based on the data submitted from the SUNLIGHT trial. The safety population included 492 patients all of whom received at least one dose of the study treatment. FTD/TPI monotherapy was administered to 246 patients and FTD/TPI in combination with bevacizumab was administered to 246 patients. During the study, safety monitoring was performed which included but were not limited to vital signs assessment, collection of hematology and chemistry laboratory tests, and ECGs. AEs were assessed on each visit using the National Cancer Institute Common Terminology Criteria for AEs

(NCI CTCAE) Version 5.0. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0.

The safety analysis is supported by data for single agent FTD/TPI TAS-102-301 (RECOURSE) trial, the pivotal randomized trial of FTD/TPI in mCRC that supported the initial approval in the US and EU, provided supportive evidence to characterize the safety of FTD/TPI monotherapy. The data from SUNLIGHT and RECOURSE were not pooled for the safety analysis.

Reviewer's comment

1. There were no significant discrepancies identified between the dataset and the information provided in the Clinical Study Report.
2. The Applicant's categorization of data and coding methods was reasonable.
3. To review the AE datasets, the following terms were pooled as per Table 15:

Table 15- Grouped and Preferred Terms Used for Analysis

Grouped term	**Preferred terms**
Abdominal pain	Abdominal discomfort Abdominal pain Abdominal pain lower Abdominal pain upper Abdominal tenderness Epigastric discomfort Hepatic pain
Acute kidney injury	Acute kidney injury Creatinine renal clearance decreased Glomerular filtration rate decreased Renal failure Renal impairment
Arrhythmia	Atrial fibrillation Atrioventricular block first degree Sinus tachycardia
Cough	Cough
Diarrhea	Colitis Diarrhea Enteritis
Dizziness	Dizziness Vertigo Vertigo positional
Dysgeusia	Dysgeusia

Grouped term	Preferred terms
Dyspnea	Dyspnea Dyspnea at rest Dyspnea exertional
Fatigue	Asthenia Fatigue
Hemorrhage	Anal hemorrhage Conjunctival hemorrhage Epistaxis Eye hemorrhage Gastritis hemorrhagic Gastrointestinal hemorrhage Gingival bleeding Hematuria Hemorrhagic stroke Rectal hemorrhage Stoma site hemorrhage Vaginal hemorrhage Wound hemorrhage
Headache	Headache
Hypertension	Blood pressure increased Hypertension
Hypotension	Hypotension
Musculoskeletal pain	Arthralgia Back pain Bone pain Musculoskeletal chest pain Musculoskeletal discomfort Musculoskeletal pain Myalgia Neck pain Non-cardiac chest pain Pain in extremity Spinal pain
Neuropathy peripheral	Dysesthesia Hypoesthesia Neuralgia Neuropathy peripheral Paranesthesia

Grouped term	Preferred terms
	Peripheral sensory neuropathy Polyneuropathy
Oedema	Generalized oedema Oedema peripheral
Pneumonia	Atypical pneumonia Para cancerous pneumonia Pneumonia Pneumonia aspiration Pneumonia streptococcal
Pneumonitis	Pneumonitis
Pyrexia	Body temperature increased Hyperthermia Pyrexia
Rash	Dermatitis Dermatitis acneiform Eczema Erythema multiforme Palmar-plantar erythrodysaesthesia syndrome Rash Rash macular Rash maculo-papular Rash pruritic
Stomatitis	Aphthous ulcer Mouth ulceration Mucosal inflammation Oral mucosal blistering Stomatitis
Urinary tract infection	Bacterial pyelonephritis Cystitis Escherichia urinary tract infection Urinary tract infection Urinary tract infection bacterial Urinary tract infection enterococcal Urinary tract infection pseudomonal
Vomiting	Retching Vomiting

Source: ADAE dataset

8.2.2 Review of the Safety Database

Overall Exposure

The median duration of treatment in the FTD/TPI plus bevacizumab arm was 5 months compared to 2 months in the FTD/TPI monotherapy arm. Correspondingly, the cumulative dose and median number of cycles were higher in the FTD/TPI plus bevacizumab arm as compared to the FTD/TPI monotherapy arm (cumulative dose 3907.4 mg/m2 vs 2246 mg/m^2, median number of cycles 5 vs 2, respectively)(Table 16).

The relative dose intensity was similar in the 2 arms, 90% and 88% in FTD/TPI monotherapy arm and FTD/TPI plus bevacizumab arm, respectively.

If treatment with FTD/TPI was delayed for patients on the combination arm, bevacizumab was not administered alone. Both drugs were restarted at the same time if treatment was resumed. If toxicity or a medical condition required discontinuation of bevacizumab therapy, FTD/TPI could be continued as monotherapy.

Table 16- Overall Exposure to FTD/TPI and FTD/TPI Plus Bevacizumab, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	**FTD/TPI plus Bev N=246 n(%)**	
		FTD/TPI	**Bevacizumab**
Treatment duration (months)			
Mean (SD)	3.4 (2.5)	6.1 (4.3)	6 (4.3)
Median (Range)	2.1 (0.6–14.3)	5 (0.1–18.5)	4.7 (0.1–18.5)
Cumulative dose (mg/m^2)			
Mean (SD)	2246.5 (1662.3)	3907.4 (2695.6)	55.1 (39.7)
Median (Range)	1387.5 (137.8–9970.5)	3309.5 (16.9–11769)	40.1 (5–170)
Number of Cycles			
Mean (SD)	3.4 (2.4)	6 (4.1)	5.9 (4.1)
Median (Range)	2 (1–15)	5 (1–17)	5 (1–17)
Relative Dose Intensity (%)			
Mean (SD)	87.3 (14.2)	85 (13.2)	86.9 (27.3)
Median (Range)	90.4 (19.7–158.4)	88.3 (15.9–103.3)	87.6 (36.4–463)

Source: adsl.xpt, adex.xpt.

All the patients randomized in the SUNLIGHT trial received the treatment assigned at the time of randomization. The safety set population was identical to the FAS (n=492). The demographics of the safety population are as below in Table 17.

Table 17- Demographics of the Safety Population, SUNLIGHT Trial

	FTD/TPI N=246	**FTD/TPI plus Bev N=246**
Median age (min, max) years	64 (24 - 90)	62 (20 - 84)
Age group, n (%)		
18 - 64 Years	129 (52)	146 (59)
≧65 - <75 Years	83 (34)	76 (31)
≥75 years	34 (14)	24 (10)
Sex, n (%)		
Male	134 (54)	122 (50)
Female	112 (46)	124 (50)
Race, n (%)		
White	220 (89)	215 (87)
Unknown	17 (7)	18 (7)
Other	5 (2)	8 (3.3)
Black	3 (1.2)	4 (1.6)
Asian	1 (0.4)	0 (0)
American Indian/Native Alaskan	0 (0)	1 (0.4)
ECOG PS at baseline, n (%)		
0	106 (43)	119 (48)
1	139 (57)	127 (52)
2	1 (0.4)	0 (0)

Source: ADSL dataset

Reviewer's comment: The baseline characteristics of the populations in the two arms were similar.

Adequacy of the safety database:

The size of the safety database and the extent of FTD/TPI plus bevacizumab exposure were adequate to assess the toxicity of FTD/TPI and bevacizumab in this patient population.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission quality was adequate for this review. The submission was clearly organized and included adequate narratives of AEs as agreed upon by the Applicant and FDA. The OSI Investigations inspected three clinical sites. No major issues were identified at any of the sites. The study was conducted according to GCP and there were no data integrity issues identified during the review of this submission

Categorization of Adverse Events

The safety and tolerability assessment of FTD/TPI monotherapy and FTD/TPI plus bevacizumab was based on the frequency of deaths, AEs, serious AEs (SAEs), AEs leading to discontinuation, AEs leading to treatment interruptions, AEs leading to dose reductions, select AEs of interest, clinical laboratory assessments (including hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. AEs were coded using MedDRA Version 25.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using random audit. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. AEs and laboratory values were grade for severity using the NCI CTCAE Version 5.0.

Treatment emergent adverse events (TEAE) are AEs with onset or worsening during the treatment period, defined as occurring between the first study treatment intake and up to 30 days after the last study treatment intake. SAEs were defined as follows: Any AE that at, any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is medically significant, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. AEs of special interest (AESI) included hypertension, proteinuria, hemorrhage/bleeding, embolic/thrombotic events, gastrointestinal perforation, and wound healing complications.

Reviewer's comment- The definitions of TEAEs and SAEs were adequate. The Applicant's predefined AESIs were considered appropriate given the known safety profile of both FTD/TPI and bevacizumab.

Routine Clinical Tests

The following routine clinical tests were collected during the SUNLIGHT trial. In general, routine laboratory tests were collected during the screening period (seven days prior to randomization) and at study withdrawal. If laboratory tests were not collected within seven days of Cycle 1 Day 1 (C1D1) they are collected again prior to start of first study treatment.

Routine hematology tests (complete blood count [CBC] and differential) were collected seven days prior to randomization or on C1D1, on C1D15, on D1 and D15 of every subsequent cycle, and at treatment withdrawal.

The following chemistry parameters – albumin, electrolytes (sodium, potassium, chloride, total calcium, magnesium, phosphate), blood urea nitrogen (BUN), serum creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, alkaline phosphatase, total bilirubin (in case of elevation in total bilirubin, fractionation [direct/indirect]), and lactate dehydrogenase (LDH)were collected seven days prior to randomization or on C1D1, on C1D15, D1 of every subsequent cycle, and at treatment withdrawal.

Coagulation parameters were checked seven days prior to randomization or on C1D1, D1 of Cycles ≥2, and at treatment withdrawal.

Urinalysis was checked seven days prior to randomization or on C1D1, on C1D15, on D1 of subsequent cycles, and at treatment withdrawal. If dipstick proteinuria was noted to be ≥2+, a 24 hours-collection urine was required, and quantitative assessment of proteinuria was performed.

Females of childbearing age had pregnancy testing with serum beta human chorionic gonadotropin (β-HCG) or highly sensitive urine test (except during screening period) seven days prior to randomization and at treatment withdrawal.

All laboratory data were graded using NCI-CTCAE Version 5.0.

8.2.4 Safety Results

Deaths

The survival cutoff date was July 19, 2022. However, the prespecified clinical cutoff for the safety analysis, which includes an analysis of deaths, was July 5, 2022. There was a total of 323 deaths at the clinical cutoff date of July 5, 2022, and 331 deaths at the survival cutoff date of July 19, 2022. Between July 5, 2022, and July 19, 2022, there were 8 deaths, all of which occurred in patients who were off treatment and in the follow-up period (after the 30-day safety follow-up). These patients died due to disease progression (N=7) and unknown cause (N=1).

Most deaths occurred in the follow-up period for both the arms (FTD/TPI monotherapy – 62%; FTD/TPI plus bevacizumab – 54%). Most deaths that occurred during the treatment period were related to disease progression except for those listed below in Table 17 18. Similarly, most deaths in the follow-up period were related to disease progression and the reason for one death in the follow-up period remained unknown.

Table 17 18– Deaths, SUNLIGHT Trial

	FTD/TPI [a] N=246 n(%)	FTD/TPI plus Bev [a] N=246 n(%)
Total Deaths	177 (72)	146 (59)
Death during treatment period (within 30 days)	24 (10)	13 (5)
Beyond 30 days after last dose	153 (62)	133 (54)

[a]DCO date: July 5, 2022
Source: ADSL

There was a total of 27 fatal TEAEs in the FTD/TPI monotherapy arm and 13 fatal TEAEs in the FTD/TPI plus bevacizumab arm. The fatal TEAEs are summarized as below in Table 18.

Table 19- TEAE leading to Death During Treatment Period or Follow-Up Period, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)
Death due to AEs	**27 (11)**	**13 (5)**
Malignant Neoplasm Progression	11 (4.5)	6 (2.4)
Hepatic Failure	3 (1.2)	0 (0)
Cachexia	2 (0.8)	0 (0)
Multiple Organ Dysfunction Syndrome	2 (0.8)	0 (0)
Cardiac Failure Acute	1 (0.4)	0 (0)
Cerebrovascular Accident	1 (0.4)	0 (0)
Covid-19	1 (0.4)	1 (0.4)
Death	1 (0.4)	0 (0)
Fatigue	1 (0.4)	0 (0)
General Physical Health Deterioration	1 (0.4)	0 (0)
Jaundice	1 (0.4)	0 (0)
Metastases To Central Nervous System	1 (0.4)	0 (0)
Respiratory Failure	1 (0.4)	0 (0)
Sub ileus	1 (0.4)	0 (0)
Urosepsis	1 (0.4)	0 (0)

	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)
Septic Shock	0 (0)	2 (0.8)
Abdominal Sepsis	0 (0)	1 (0.4)
Cardiac Failure	0 (0)	1 (0.4)
Cardiac Failure Congestive	0 (0)	1 (0.4)
Covid-19 Pneumonia	0 (0)	1 (0.4)
Intestinal Obstruction	0 (0)	1 (0.4)

Source: ADSL and ADAE datasets

According to the Applicant, of the fatal TEAEs 8 of 13 and 22 of 27 occurred in the FTD/TPI plus bevacizumab arm and the FTD/TPI monotherapy arm; respectively. The other 5 deaths in each study arm were not attributed or considered to be study drug-related as per the Applicant. Upon review of the death narratives of the fatal TEAEs not considered by the Applicant to be disease progression, it was determined by the FDA that the following patient's fatal TEAEs were unlikely to be due to disease progression and could possibly be treatment-related.

FTD/TPI plus bevacizumab arm:

(b) (6) - 62-year-old male with metastatic rectal adenocarcinoma with peritoneal, lung, liver, and lymph node metastases. On (b) (6), the patient received the first dose of FTD/TPI and bevacizumab. Last dose of FTD/TPI was on (b) (6), and bevacizumab on (b) (6). On (b) (6), the patient was admitted with grade 3 **rectal fistula**. He subsequently developed sepsis and died. Fistula formulation can be an AE from bevacizumab and the fatal AE should be considered a treatment-related AE.

(b) (6) – 53-year-old male with metastatic descending colon adenocarcinoma with lung and liver metastasis, diagnosed (b) (6). Patient started FTD/TPI and bevacizumab on (b) (6). Thirteen days after the last dose of bevacizumab and 11 days after last dose of FTD/TPI, the patient presented with severe anemia (hemoglobin 7.7) and pericarditis which was thought to be related to disease progression, patient was subsequently admitted later that week for congestive heart failure and also diagnosed with decompensated atrial fibrillation. Thirty-six days after last dose of bevacizumab and 28 days after last dose of FTD/TPI, the patient died from heart failure secondary to **decompensated atrial fibrillation**.

(b) (6) - 58-year-old male with metastatic colorectal adenocarcinoma of the sigmoid with liver, bone, and peritoneal metastasis at diagnosis in (b) (6). Patient received first dose of FTD/TPI and bevacizumab on (b) (6). On Cycle 2, Day 9, which was 8 days after the last dose of bevacizumab and 1 day after the last dose of FTD/TPI, the patient experienced bowel perforation which may have been an AE from bevacizumab. The patient died 9 days later due to sepsis from **bowel perforation**.

FTD/TPI arm:

(b) (6) - 65-year-old male with metastatic rectal adenocarcinoma with lymph node, lung, and liver metastasis. Patient started FTD/TPI on (b) (6). On (b) (6), 24 days after last intake of Cycle 4, patient passed away and **no cause of death** was available.

(b) (6) - 76-year-old female with mCRC with liver metastasis. The patient started on FTD/TPI on (b) (6). Patient started Cycle 9 was on (b) (6) and on (b) (6), patient died suddenly and reported cause was **respiratory failure**.

(b) (6) - 65-year-old male with mCRC with lung, peritoneal, soft tissue, and adrenal glands metastases. Patient started FTD/TPI on (b) (6), and 3 days later experienced Grade 4 **stroke** and passed away.

(b) (6) - 71-year-old male with history of spindle-shaped aneurysm of the abdominal aorta and metastatic rectal adenocarcinoma with lung metastasis. Patient was started on FTD/TPI on (b) (6). He developed worsening anemia while on treatment requiring packed red blood cells (pRBC) blood transfusion on (b) (6). On (b) (6), hemoglobin was still low at 9.4 g/dl (11 g/dl at start of Cycle1), and on (b) (6), patient suddenly passed away at home after experiencing pronounced weakness and was thought to have **acute heart failure** which did not respond to resuscitation by the emergency medical personnel. Anemia is a known AE of FTD/TPI and can precipitate heart failure.

Reviewer's comment- Most fatal AEs observed in both study arms appear to be related to disease progression which is expected in this setting of third-line treatment for mCRC. The four deaths in the FTD/TPI monotherapy arm and three deaths in the FTD/TPI plus bevacizumab arm may have been related to the drug. Although these deaths may possibly be related to study treatment, they do not appear to suggest a new safety signal.

Serious Adverse Events

SAEs were more common in the FTD/TPI monotherapy arm compared to the FTD/TPI plus bevacizumab arm, at 31% and 25%, respectively (Table 20). The most common SAEs (≥2%) in the FTD/TPI plus bevacizumab arm included intestinal obstruction (2.8%) and COVID-19 (2.0%).

Table 20- Serious Adverse Events, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	**FTD/TPI plus Bev N=246 n(%)**
Patients with serious AEs	**77 (31)**	**61 (25)**
Infections And Infestations		
Covid-19	6 (2.4)	5 (2.0)

	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)
Pneumonia*	2 (0.8)	3 (1.2)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)		
Malignant Neoplasm Progression	11 (4.5)	6 (2.4)
Metastases To CNS	4 (1.6)	0 (0)
Gastrointestinal Disorders		
Intestinal Obstruction	5 (2.0)	7 (2.8)
Abdominal Pain*	3 (1.2)	4 (1.6)
Diarrhea*	3 (1.2)	1 (0.4)
Hepatobiliary Disorders		
Hepatic Failure	5 (2.0)	0 (0)
Jaundice	5 (2.0)	2 (0.8)
General Disorders and Administration Site Conditions		
Fatigue*	3 (1.2)	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders		
Pulmonary Embolism	4 (1.6)	1 (0.4)
Vascular Disorders		
Hemorrhage*	3 (1.2)	4 (1.6)

**Represents a composite of multiple related terms*
Source: ADSL and ADAE

Reviewer's comment- There was not a clinically meaningful numerical increase in SAEs observed on the FTD/TPI monotherapy arm compared to the FTD/TPI plus bevacizumab arm. No new safety signal for SAEs was noted.

Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of TEAEs leading to treatment discontinuation was the same in both arms at 13% (31/246 in each arm). The most common AEs (at least 2 events in either arm) leading to withdrawal of FTD/TPI in the FTD/TPI monotherapy arm vs FTD/TPI plus bevacizumab arm included fatigue 1.2% vs 3.7%, abdominal pain 1.2% vs 0.4%, jaundice 0.8% each arm, intestinal obstruction 0.8% vs 0.4%, and pain 0.8% vs 0, respectively for the FTD/TPI monotherapy arm vs the FTD/TPI plus bevacizumab arm. AEs leading to withdrawal of bevacizumab occurred in 15% of the patients (36/246) and the most common AEs ($\geq$2 events) included fatigue 3.7%; abdominal pain, biliary dilatation decrease in appetite, pain, proteinuria, and pulmonary embolism (0.8% each).

Dose Reductions and Interruptions Due to Adverse Events

The dose of FTD/TPI was reduced in 8% of patients in the FTD/TPI monotherapy arm and 7% of patients in the FTD/TPI plus bevacizumab arm. The most common AEs (≥2 events in either arm) leading to dose reduction of FTD/TPI in the FTD/TPI monotherapy arm vs FTD/TPI plus bevacizumab arm were diarrhea (2% vs 0.4%), fatigue (1.6% vs 0.8%), vomiting (0.8% vs 0) and decease in platelet count (0.8% vs 0), respectively.

Dose delays refer to doses that were given; however, the administration of the dose was postponed from the scheduled treatment date. Treatment interruptions were considered to be lost treatment days that resulted in missed doses that were not replaced.

The incidence of TEAEs leading to a delay in treatment with FTD/TPI was 60% in the FTD/TPI monotherapy arm and 68% in the FTD/TPI plus bevacizumab arm. The most common TEAEs (≥2%) leading to treatment delay for FTD/TPI in FTD/TPI monotherapy arm vs FTD/TPI plus bevacizumab arm included neutropenia (41% vs 48%) or decrease in neutrophil count (6% vs 12%), anemia (4% vs 2%), fatigue (2.4% vs 2%), thrombocytopenia (2.4% vs 2.8%), leukopenia (2% vs 0.8%) and urinary tract infection (2% each), respectively. Bevacizumab was delayed in 70% of the patients and the most common AEs leading to delay was neutropenia (50%) or decrease in neutrophil count (12%).

Treatment interruption of FTD/TPI due to an TEAE occurred in 9% of patients in the FTD/TPI monotherapy arm and 11% of the FTD/TPI plus bevacizumab arm. The most common TEAEs (≥1%) leading to treatment interruption of FTD/TPI in the FTD/TPI monotherapy arm vs FTD/TPI plus bevacizumab arm was nausea (0.8% vs 2.8%) and diarrhea (1.2% vs 0.4%), respectively.

Table 21- Treatment Modifications, SUNLIGHT Trial

	FTD/TPI N=246 n(%)	**FTD/TPI plus Bev N=246 n(%)**
TEAE leading to drug withdrawn (FTD/TPI)	31 (13)	31 (13)
TEAE leading to drug reduction (FTD/TPI)	20 (8)	18 (7)
TEAE leading to treatment delayed (FTD/TPI)	147 (60)	167 (68)
TEAE leading to treatment interruption (FTD/TPI)	21 (9)	27 (11)
Treatment delayed and reduced FTD/TPI -due to AEs	11 (4.5)	31 (13)
TEAE leading to drug withdrawn bevacizumab	-	36 (15)

	FTD/TPI N=246 n(%)	FTD/TPI plus Bev N=246 n(%)
TEAE leading to drug interruption-bevacizumab	-	64 (26)
TEAE leading to treatment delay- bevacizumab	-	172 (70)

Source: ADSL and ADAE datasets

Reviewer's comment- Overall the incidence of TEAEs leading to treatment withdrawal, delay, interruption, or dose reduction were comparable in the two arms. Although FDA evaluated laboratory abnormalities, such as hematologic AEs, based on data that is provided in the analysis dataset for laboratory results, it should be noted that myelosuppression contributed to most cases of delay, interruption, and dose reduction, the rates of which were similar in the two arms. Myelosuppression is a known AE associated with FTD/TPI.

Treatment Emergent Adverse Events and Adverse Reactions

Almost all patients in both arms experienced a TEAE (98% in each arm) (Table 22). The most common TEAEs observed in patients treated with FTD/TPI plus bevacizumab were fatigue, nausea and diarrhea.

All grades of nausea were 10% higher in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm at 37% and 27%, respectively, however Grade ≥3 nausea was low in both arms, at 1.6% each.

All grades of fatigue (45% vs 37%), musculoskeletal pain (18% vs 11%), and decreased appetite (20% vs 15%) were more common in the FTD/TPI plus bevacizumab arm compared to FTD/TPI monotherapy arm. However, incidence of Grade ≥3 AEs of fatigue (5% vs 8%), musculoskeletal pain (1.2% vs 2%), and decreased appetite (0.8% vs 1.2%) were slightly lower in in the FTD/TPI plus bevacizumab arm as compared to the FTD/TPI monotherapy arm.

In general, the incidence of Grade 3-4 events observed with FTD/TPI plus bevacizumab were numerically low and appeared consistent with the experience with single agent FTD/TPI in the RECOURSE trial and with the FTD/TPI control arm in the SUNLIGHT trial (with exceptions note above).

Table 22-Treatment Emergent Adverse Events ≥10% of Patients, SUNLIGHT Trial

Adverse Reactions	FTD/TPI plus Bev N=246 (%)		FTD/TPI N=246 (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Gastrointestinal disorders				

Adverse Reactions	**FTD/TPI plus Bev N=246 (%)**		**FTD/TPI N=246 (%)**	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nausea	37	1.6	27	1.6
Diarrhea*	21	1.2	19	2.4
Abdominal pain*	20	2.8	18	3.7
Vomiting*	19	0.8	15	1.6
Stomatitis*	13	<0.4	4.1	0
Constipation	11	0	11	0.8
General disorders and administration site conditions				
Fatigue*	45	5	37	8
Pyrexia	4.9	0	6	0.4
Infections and infestations*	31	8	24	8
Metabolism and nutrition disorders				
Decreased appetite	20	<0.8	15	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	18	1.2	11	2
Nervous system disorder				
Headache	8	0	3.7	0
Vascular disorders				
Hypertension*	11	6	2	1.2
Hemorrhage*	10	1.2	3.7	0.8
Renal and urinary disorders				
Proteinuria	6	0.8	1.2	0

**Represents a composite of multiple related terms*
Source: Reviewer analysis- ADSL and ADAE datasets

Reviewer's comment: In the SUNLIGHT trial, the overall incidence of all grade TEAEs is similar in both study arms. Gastrointestinal disorders, which are known side effects with FTD/TPI, were slightly higher in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI arm. It is noted that the median duration of treatment was longer on the FTD/TPI plus bevacizumab arm compared to the FTD/TPI arm, which is thought to be related to the delay in disease progression.

Laboratory Findings

Laboratory values were graded according to CTCAE v 5.0, and evaluation of laboratory abnormalities was based on the worst grade of each laboratory event compared to the baseline laboratory value.

Table 22 - All Grade Laboratory Abnormalities Occurring in ≥10% of Patients, SUNLIGHT Trial

	FTD/TPI N=246 n(%)		FTD/TPI plus Bev N=246 n(%)	
Laboratory Test*	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hematology				
Anemia	179 (73)	27 (11)	164 (68)	13 (5)
Neutropenia	164 (68)	93 (39)	195 (81)	125 (52)
Thrombocytopenia	69 (29)	2 (0.8)	131 (54)	10 (4.1)
Chemistry				
Alkaline Phosphatase increased	86 (36)	3 (1.2)	75 (31)	2 (0.8)
AST increased	68 (28)	3 (1.2)	8 (34)	5 (2.1)
ALT increased	56 (23)	1 (0.4)	79 (33)	8 (3.3)
Sodium decreased	48 (20)	8 (3.3)	60 (25)	5 (2.1)
Creatinine increased	35 (14)	0 (0.0)	28 (12)	2 (0.8)
Potassium increased	36 (15)	0 (0.0)	42 (17)	0 (0.0)
Potassium decreased	29 (12)	6 (2.5)	30 (12)	2 (0.8)

[*]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: FTD/TPI plus bevacizumab group (range: n= 242) and FTD/TPI group (range: 240 to 242).
Source: Reviewer analysis- ADSL and ADLB

Reviewer's comment- Hematological lab abnormalities of neutropenia and thrombocytopenia were numerically higher in the FTD/TPI plus bevacizumab arm and numerically lower for anemia compared to the FTD/TPI monotherapy arm. The higher incidence of myelosuppression in the FTD/TPI plus bevacizumab arm may be due to the longer treatment duration observed on the FTD/TPI plus bevacizumab arm. Lab changes in chemistry were not increased in the treatment arm.

Vital Signs

Patient's vital signs (blood pressure, heart rate, body temperature) and body weight were measured at the following time points:

- within 7 days prior to randomization,
- C1D1 prior to study treatments administration only if there is more than 7 days since screening assessment,
- C1D15;
- Beginning with cycle 2, and for all subsequent cycles,
    - D1, obtain within 48 hours prior to study treatments administration,
    - D15 (only for patients in the FTD/TPI plus bevacizumab arm), obtain within 48 hours prior to bevacizumab administration, and
- withdrawal visit.

There were no clinically meaningful changes in vital sign measurements over the course of the trial.

Electrocardiograms (ECGs)

ECGs were not performed routinely during the SUNLIGHT trial. A 12-lead resting ECG was obtained prior to patient signing the ICF within the 28 days prior to randomization and again at the withdrawal visit, which occurred within 4 weeks after treatment discontinuation.

QT

An ECG substudy was included in the submission that supported the original approval in order to assess effects on cardiac electrophysiology. At the time of the review of the original submission the FDA QT-IRT team concluded that FTD/TPI is unlikely to cause clinically relevant QT prolongation.

Immunogenicity

Not applicable

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest (AESI)

AESI include hypertension, proteinuria, hemorrhage/bleeding, embolic/thrombotic events, gastrointestinal perforation, and wound healing complications, which are adverse reaction known to be associated with treatment with bevacizumab. A higher incidence of all Grades of these AEs, except for delayed wound healing, was noted in the bevacizumab containing arm. Overall, the incidence of Grade ≥3 events in the FTD/TPI plus bevacizumab arm was low and did not appear to occur at a disproportionately higher rate compared to the FTD/TPI monotherapy arm. However, Grade ≥3 hypertension was observed at a numerically higher rate of 6% (15 events). (Table 23).

Table 23 – Adverse Events of Special Interest, SUNLIGHT Trial

	FTD/TPI N=246 n(%)		FTD/TPI plus Bev N=246 n(%)	
AE of Special Interest	**All grades**	**Grade 3-5**	**All grades**	**Grade 3-5**
Hypertension	5 (2)	3 (1)	27 (11)	15 (6)
Hemorrhage	9 (4)	2 (1)	29 (12)	3 (1)
Embolic and thrombotic events	9 (4)	8 (3)	12 (5)	4 (2)
Proteinuria	3 (1)	0 (0)	15 (6)	2 (1)
GI Perforation	0 (0)	0 (0)	6 (2)	4 (2)
Wound healing complications	0 (0)	0 (0)	0 (0)	0 (0)

Source: adae.xpt, adsl.xpt.

Reviewer's comments: AESIs of hypertension, proteinuria, hemorrhage, GI perforation, and embolic and thrombotic events were higher in the bevacizumab containing arm consistent with the known safety profile associated with bevacizumab. The incidence of these AESI did not appear to be higher than what has been observed for bevacizumab (7).

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

QoL was assessed based on the EORTC QLQ-C30 and EQ-5D-5L assessment instruments. Patients completed the EORTC QLQ-C30 questionnaire and EQ-5D-5L at the beginning of each visit for the following study timepoints:

- within 7 days prior to randomization (baseline),
- at Day 1 of cycles ≥ 2 (every cycle) prior to any study procedure, and
- at the withdrawal visit.

EORTC QLQ-C30

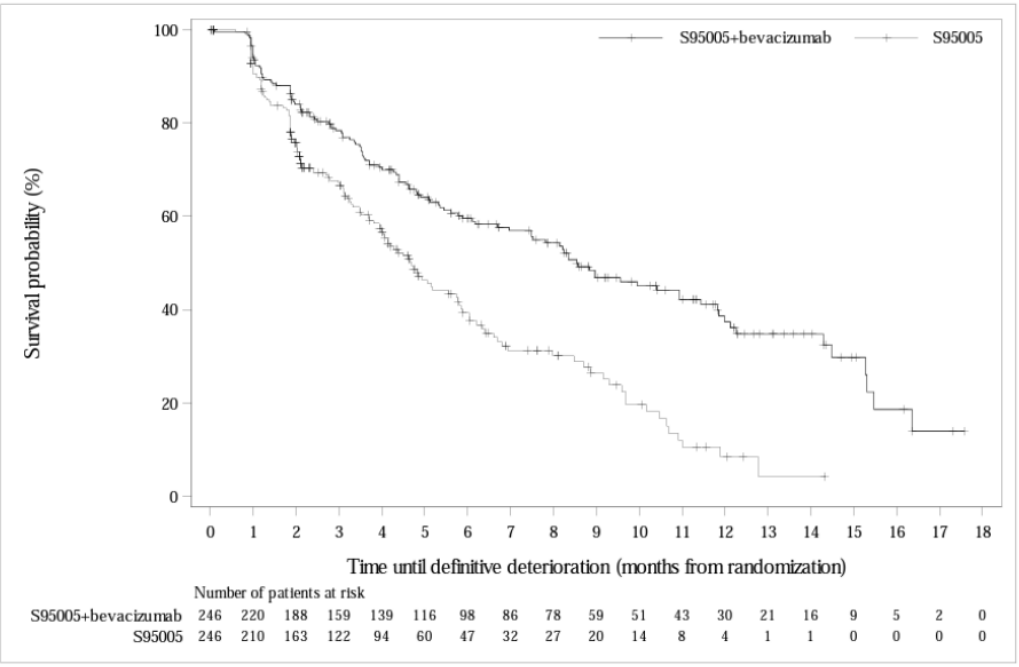
The Applicant analyzed QoL scores based on a change from baseline. Changes in the GHS was the primary QoL variable of interest to the Applicant. An absolute change from baseline greater than 10 points in the EORTC QLQ-C30 was considered clinically meaningful. The only relevant change noted was that of appetite loss at Cycle 4 which showed a mean change of 11.2 ± 32.7 in the FTD/TPI monotherapy arm and 9.0 ± 26.5 in the FTD/TPI plus bevacizumab arm.

The proportion of patients with worsening from baseline of less than 10 points in the GHS score was comparable in the two arms: 57% in the FTD/TPI monotherapy arm and 61% in the FTD/TPI

plus bevacizumab arm.

There were more patients in the FTD/TPI monotherapy arm compared to the FTD/TPI plus bevacizumab arm who reported definitive deterioration (≥10 points) of GHS score (57% vs 49%). For all QoL items, the median time until definitive deterioration of 10 points (TUDD) was longer in the FTD/TPI plus bevacizumab arm than in the FTD/TPI monotherapy arm (Figure 5).

Figure 5- Time Until Definitive Deterioration in the GHS Score, SUNLIGHT Trial



Source: SUNLIGHT CSR Figure (11.3.2.1) 1

EQ-5D-5L

The dimensional 5-level system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) was converted into a single index utility score. The EQ-5D-5L measure includes also a visual analogue scale (VAS) with 100 as best imaginable health state and 0 as worst imaginable health state.

The EQ-5D-5L score at baseline was similar in the two study arms: 0.940 in the FTD/TPI monotherapy arm and 0.942 in the FTD/TPI plus bevacizumab arm. The median change from baseline in EQ-5D-5L utility score was null in the two arms up to 8 cycles.

The mean (median) VAS was similar at baseline in the two arms: 67.6 ± 19.1 (70.0) in the FTD/TPI monotherapy arm and 69.8± 18.6 (71.0) in the FTD/TPI plus bevacizumab arm. The change from baseline was not different between the two arms.

An analysis of deterioration of performance status was also conducted from randomization to

worsening of ECOG PS to ≥2. The median time to worsening of ECOG PS to ≥2 was 6.3 months (95% CI: 5.55,7.23) in the FTD/TPI monotherapy arm and 9.3 months (95% CI: 8.34, 10.61) in the FTD/TPI plus bevacizumab arm. In the FTD/TPI monotherapy arm, 25 (10%) patients deteriorated to a worst ECOG PS of 2, 13 (5%) patients deteriorated to a worst ECOG PS of 3, and 1 (0.4) patient deteriorated to a worst ECOG PS of 4.

In the FTD/TPI plus bevacizumab arm, 23 (10%) patients deteriorated to a worst ECOG PS of 2, and 4 (1.7%) patients deteriorated to a worst ECOG PS of 3.

Reviewer's comment: A longer median time to worsening ECOG PS from 0 to 1 to ≥2 was observed in the FTD/TPI plus bevacizumab arm compared to the FTD/TPI monotherapy arm. No relevant mean change from baseline was observed in either arm for QoL scores per the EORTC QLQ-C30. The combination FTD/TPI plus bevacizumab appears to have maintained GHS without clinical deterioration for a longer time than FTD/TPI monotherapy. Analyses of patient QoL per the EORTC QLQ-C30 were not formally tested and are considered exploratory.

8.2.7 Safety Analyses by Demographic Subgroups

Age

Differences of ≥10% between patients <65 years and ≥65 years and by treatment arm are reported below.

Grade ≥3 AEs were more common in patients age ≥65 years compared to patients <65 years of age for both the FTD/TPI monotherapy arm (76% vs 64%) and the FTD/TPI plus bevacizumab arm (77% vs 69%). Grade ≥3 neutropenia was increased in patients ≥65 years compared to patients <65 years for both the FTD/TPI monotherapy arm (45% vs 33%) and the FTD/TPI plus bevacizumab arm (60% vs 46%). The incidence of Grade ≥3 thrombocytopenia was increased in patients age ≥65 years compared to patients age < 65 years in the FTD/TPI plus bevacizumab arm (5% vs 3.5%).

Sex

Differences of ≥10% between male and female patients and by treatment arm are reported below.

Grade ≥3 neutropenia was more common in male patients compared to female patients in the FTD/TPI monotherapy arm (37% vs 27%). FDA did not identify difference in baseline demographic characteristics, such as age or ECOG PS, that might account for this. All Grades of nausea were higher in females (45%) compared to males (29%) in the FTD/TPI plus bevacizumab arm.

ECOG at baseline

Patients enrolled in the SUNLIGHT trial had an ECOG PS at baseline of either 0 or 1. (Except one patient in the FTD/TPI monotherapy arm with ECOG PS of 2)

Differences of ≥10% between the subgroups of patients with ECOG PS 0 and ECOG PS ≥1 and by treatment arm are reported below.

Serious TEAEs were observed at a higher rate for patients with ECOG PS ≥1 than for patients with ECOG PS 0 on both the FTD/TPI plus bevacizumab arm (30% vs 19%) and the FTD/TPI monotherapy arm (36% vs 25%). TEAEs leading to death in the FTD/TPI monotherapy arm were also higher in patients with a ECOG PS ≥1 compared to patients with an ECOG PS 0 (14% or 20 deaths vs 7% or 7 deaths). Ten of the 20 deaths in the ECOG PS ≥1 subgroup in the FTD/TPI monotherapy arm were attributed to malignant neoplasm progression.

Creatinine Clearance at Baseline

The study enrolled patients with creatinine clearance ≥50 mL/min, assessed using the Cockcroft & Gault formula.

Most patients had normal renal function (creatinine clearance [CrCl] ≥90 mL/min; 54%) or mild renal impairment (CrCl 60-89 mL/min; 34%) at baseline; moderate renal impairment (CrCl 30-59 mL/min) was reported for 12% of patients.

Only 28 out of 246 in the FTD/TPI monotherapy arm and 30 out of 246 patients in the FTD/TPI plus bevacizumab arm had a creatinine clearance <60ml/min. Differences between subgroups of patients with CrCl <60 ml/min and ≥60 ml/min and by treatment arm are reported below.

Serious or Grade ≥3 TEAEs were ≥10% higher in the CrCl <60 ml/min subgroup than in the CrCl ≥ 60 ml/min subgroup for both the FTD/TPI plus bevacizumab arm (40% vs 23%) and for the FTD/TPI monotherapy arm (89% vs 67%).

Race

Approximately 90% of patients enrolled in the SUNLIGHT trial reported White race; this precludes analyses of safety by race subgroups (Table 24).

Table 24- Distribution of Patients by Race, SUNLIGHT study

Race n (%)	**FTD/TPI N=246 n(%)**	**FTD/TPI plus Bev N=246 n(%)**
White	220 (89)	215 (87)
Black	3 (1.2)	4 (1.6)
Asian	1 (0.4)	0 (0)
American Indian/native Alaskan	0 (0)	1 (0.4)
Other	5 (2.0)	8 (3.3)

Source: ADSL

Reviewer's comment- Overall an increase in TEAEs was noted with factors which are expected to increase the risk of experiencing an AE such as increasing age, poor ECOG PS and lower creatinine clearance. A higher incidence of Grade ≥3 neutropenia was noted in females compared to males in the FTD/TPI monotherapy arm, despite no difference in baseline ECOG PS or age, which is unexplained. There was more nausea experienced by females compared to males which has been well described with other chemotherapy agents. Although increasing age, decreasing ECOG and lower creatinine clearance appear to be baseline characteristics that increase the risk of AEs, the overall safety profile observed in these demographic subgroups appears to be generally consistent with that observed in the entire patients population and with what has been observed with FTD/TPI and bevacizumab when administered as single agents.

In a pooled analysis of 868 patients from the RECOURSE and TAGS trials, patients who were ≥65 years of age or older who received FTD/TPI had a higher incidence of hematologic laboratory abnormalities compared to patients <65 years. There did not appear to be differences in effectiveness in patients treated with FTD/TPI who were ≥65 years compared to those who were <65 years.

8.2.8 Specific Safety Studies/Clinical Trials

No studies were performed to address specific safety concerns.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

No additional safety explorations related to human reproduction and pregnancy were performed during this review. Refer to the USPI for available information about use in individuals who are pregnant, lactating or capable of human reproduction.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of FTD/TPI in pediatric patients have not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There were no new safety concerns identified in the postmarket setting that were updated in this submission.

Expectations on Safety in the Postmarket Setting

FTD/TPI is approved for the treatment of multiple malignancies and its safety profile is well characterized. No new safety signals that appear relevant to the proposed indication in this supplemental NDA have been identified.

8.2.11 Integrated Assessment of Safety

The Applicant provided side by side tabular comparisons for hematological and non-hematological AEs for FTD/TPI in the SUNLIGHT, RECOURSE and TAGS clinical trials (Table 25, Table 26).

In general, the incidences of the common non-hematological toxicities, such as nausea, decrease in appetite, fatigue, diarrhea, vomiting, abdominal pain, constipation, and pyrexia, were lower in the FTD/TPI monotherapy arm of the SUNLIGHT trial compared to those noted in the RECOURSE and TAGS studies.

Table 25- Tabular Comparison of TEAEs in the FTD/TPI Monotherapy Arm, SUNLIGHT, RECOURSE and TAGS Trials

Preferred Term	FTD/TPI – SUNLIGHT (N=246) n (%)		FTD/TPI – RECOURSE (N=533) n (%)		FTD/TPI – TAGS (N=335) n (%)		FTD/TPI SUNLIGHT + RECOURSE + TAGS (N=1114) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with at least one AE	**241 (98.0)**	**171 (69.5)**	**524 (98.3)**	**370 (69.4)**	**326 (97.3)**	**267 (79.7)**	**1091 (97.9)**	**808 (72.5)**
Nausea	67 (27.2)	4 (1.6)	258 (48.4)	10 (1.9)	124 (37.0)	10 (3.0)	449 (40.3)	24 (2.2)
Decreased appetite	38 (15.4)	3 (1.2)	208 (39.0)	19 (3.6)	115 (34.3)	29 (8.7)	361 (32.4)	51 (4.6)
Fatigue	40 (16.3)	9 (3.7)	188 (35.3)	21 (3.9)	89 (26.6)	23 (6.9)	317 (28.5)	53 (4.8)
Diarrhoea	46 (18.7)	6 (2.4)	170 (31.9)	16 (3.0)	76 (22.7)	9 (2.7)	292 (26.2)	31 (2.8)
Vomiting	36 (14.6)	4 (1.6)	148 (27.8)	11 (2.1)	83 (24.8)	12 (3.6)	267 (24.0)	27 (2.4)
Asthenia	55 (22.4)	10 (4.1)	97 (18.2)	18 (3.4)	65 (19.4)	16 (4.8)	217 (19.5)	44 (3.9)
Abdominal pain	27 (11.0)	4 (1.6)	79 (14.8)	11 (2.1)	55 (16.4)	14 (4.2)	161 (14.5)	29 (2.6)
Constipation	28 (11.4)	2 (0.8)	81 (15.2)	1 (0.2)	45 (13.4)	4 (1.2)	154 (13.8)	7 (0.6)
Pyrexia	15 (6.1)	1 (0.4)	98 (18.4)	6 (1.1)	25 (7.5)	0	138 (12.4)	7 (0.6)

Source: SUNLIGHT CSR Table (12.1.1) 2, Section 15.3.1.1; TAGS ISS Table 14.3.1.1

The incidence of hematological toxicity for anemia, thrombocytopenia, leukopenia and lymphopenia was higher in the RECOURSE and TAGS study compared to the FTD/TPI monotherapy arm in the SUNLIGHT study.

Table 26- Tabular Comparison of Hematological Adverse Events in FTD/TPI Monotherapy Arm of SUNLIGHT, RECOURSE and TAGS Trials.

Table 40: Hematologic Laboratory Abnormalities – FTD/TPI Monotherapy – SUNLIGHT, RECOURSE, and TAGS

	FTD/TPI – SUNLIGHT (N=246) n (%)		FTD/TPI – RECOURSE (N=533) n (%)		FTD/TPI – TAGS (N=335) n (%)		FTD/TPI SUNLIGHT + RECOURSE + TAGS (N=1114) n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All								
Anemia	176 (73.3)	27 (11.3)	404 (76.5)	96 (18.2)	206 (62.8)	61 (18.6)	786 (71.7)	184 (16.8)
Neutropenia	163 (67.6)	93 (38.6)	353 (66.9)	200 (37.9)	217 (66.2)	125 (38.1)	733 (66.8)	418 (38.1)
Thrombocytopenia	69 (28.6)	2 (0.8)	223 (42.2)	27 (5.1)	113 (34.5)	19 (5.8)	405 (36.9)	48 (4.4)
Leukopenia	167 (69.3)	33 (13.7)	407 (77.1)	113 (21.4)	237 (72.3)	69 (21.0)	811 (73.9)	215 (19.6)
Lymphopenia	134 (55.6)	29 (12.0)	344 (65.9)	112 (21.5)	192 (58.5)	62 (18.9)	670 (61.4)	203 (18.6)

Source: SUNLIGHT CSR Section 15.3.3.2; TAGS ISS Table 14.4.4.4, Table 14.4.1.2
Abbreviations: FTD=trifluridine; N=number of patients by arm; TPI=tipiracil hydrochloride

A tabular side-by-side comparison from the SOLSTICE study was provided for FTD/TPI plus bevacizumab (Table 27).

Table 27- Tabular Comparison of FTD/TPI Plus Bevacizumab, SUNLIGHT and SOLSTICE Trials

Adverse Events (TEAEs)	FTD/TPI + Bev - SUNLIGHT (N=246) n (%)		FTD/TPI + Bev - SOLSTICE (N=423) n (%)		
	All Grades	Grade ≥3	All Grades	Grade 3	Grade 4
General					
Asthenia	60 (24.4)	10 (4.1)	95 (22)	25 (6)	1 (<1)
Fatigue	53 (21.5)	3 (1.2)	101 (24)	25 (6)	0
Gastrointestinal					
Nausea	91 (37.0)	4 (1.6)	148 (35)	7 (2)	0
Diarrhea	51 (20.7)	2 (0.8)	154 (36)	30 (7)	0
Vomiting	46 (18.7)	2 (0.8)	68 (16)	7 (2)	0
Abdominal Pain	29 (11.8)	5 (2.0)	50 (12)	7 (2)	0
Stomatitis	27 (11.0)	1 (0.4)	55 (13)	6 (1)	0
Metabolism and nutrition					
Decreased Appetite	50 (20.3)	2 (0.8)	95 (22)	6 (1)	1 (<1)
Hematologic Toxicities					
Anemia	71 (28.9)	15 (6.1)	188 (44)	58 (14)	2 (<1)
Neutropenia	153 (62.2)	106 (43.1)	278 (66)	151 (36)	69 (16)
Thrombocytopenia	42 (17.1)	7 (2.8)	81 (19)	14 (3)	2 (<1)

Source: SUNLIGHT CSR Table (12.1.1) 2, Section 15.3.1.1; Andre 2022

Reviewer's comment- The overall incidence of all Grade TEAEs and Grade ≥3 TEAEs were numerically lower in the SUNLIGHT trial for the FTD/TPI monotherapy arm compared to the FTD/TPI arms in the RECOURSE and TAGS Trials, but patients with gastric cancer generally have a shorter life expectancy and have more comorbidities. Differences between the SUNLIGHT and RECOURSE trials may be attributed to the inherent heterogeneity in trial populations, physician's experience in the management of AEs, heterogeneity in reporting, etc. Despite the differences in the patient population enrolled in the SOLSTICE trial compared to the SUNLIGHT trial, no new safety issues were identified in the FTD/TPI plus bevacizumab arm in the SUNLIGHT study.

8.3 Statistical Issues

There were no major statistical issues in the review of this application.

The SUNLIGHT trial demonstrated a statistically significant benefit for the primary endpoint of OS, with a hazard ratio of 0.61 (95% CI: 0.49, 0.77) and median OS of 10.8 months (95% CI: 9.4, 11.8) in the FTD/TPI plus bevacizumab arm compared to 7.5 months (95% CI: 6.3, 8.6) in the FTD/TPI monotherapy arm. These results are supported by the results of the key secondary

endpoint of PFS assessed by investigator, with a hazard ratio of 0.44 (95% CI: 0.36, 0.54) and median PFS of 5.6 (95% CI: 4.5, 5.9) in the FTD/TPI plus bevacizumab arm compared to 2.4 months (95% CI: 2.1, 3.2) in the FTD/TPI monotherapy arm.

PRO endpoints, including time to definitive deterioration, are considered exploratory and do not provide evidence of efficacy or tolerability.

Subgroup analyses of OS conducted without formal testing are considered exploratory. The results observed in some subgroups with small sample sizes may result in imprecise estimates and wide confidence intervals. Therefore, these results should be interpreted with caution.

8.4 Conclusions and Recommendations

The data submitted from the adequate and well-controlled SUNLIGHT trial, provides substantial evidence of the effectiveness of FTD/TPI plus bevacizumab for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. The results of the primary analysis demonstrate that patients treated with FTD/TPI plus bevacizumab had a statistically significant and clinically meaningful improvement in OS compared to patients treated with FTD/TPI (HR=0.61 (95% CI: 0.49, 0.77), with a median OS of 10.8 months (95% CI: 9.4, 11.8) compared to 7.5 months (95% CI: 6.3, 8.6)), respectively. The effect on OS was supported by the analysis of Investigator-assessed PFS (HR=0.44 [95% CI: 0.36, 0.54]).

The safety profile of FTD/TPI in combination with bevacizumab observed in the SUNLIGHT trial is acceptable for the indicated population with refractory mCRC previously heavily pre-treated. The size of the safety database as well the duration of exposure to FTD/TPI plus bevacizumab was sufficient to characterize the safety of the combination for treatment of a serious and life-threatening condition. The proportion of patients that had treatment discontinued due to AEs was low and similar in both arms of the study. Overall AEs noted in both arms as well as the AESI observed in the combination arm were consistent with the known safety profile of FTD/TPI and bevacizumab. The addition of bevacizumab to FTD/TPI did not demonstrate a new safety signal or additive toxicity to the known safety profile of FTD/TPI or that of bevacizumab.
All disciplines agree that FTD/TPI plus bevacizumab has a favorable risk-benefit profile that supports the regular approval of FTD/TPI plus bevacizumab for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

X

Yin Ren
Primary Statistical Reviewer

X

Anup Amatya
Statistical Team Leader

X

Geetika Srivastava
Primary Clinical Reviewer

X

Jamie Brewer
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this application to the Oncologic Drugs Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this NDA as no significant review issues were identified during the review of this application.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

The Applicant requested and FDA granted, a full waiver of the requirement to conduct pediatric studies based on the rarity of colon cancer in pediatric patients and the infeasibility of conducting studies in the pediatric population.

APPEARS THIS WAY
ON ORIGINAL

11 Labeling Recommendations

11.1 Prescription Drug Labeling

Table 28 summarizes changes to the proposed prescribing information (PI) made by the FDA. See the final approved prescribing information for LONSURF (FTD/TPI) accompanying the approval letter for more information.

Table 28: Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant Proposed Labeling**	**FDA Proposed Labeling**
Highlights	Updates proposed to reflect new indication and adverse reactions for combination	Minor revision to indication to align with FPI. Most common adverse events and laboratory abnormalities were added.
Full Prescribing Information		
Section 1: Indications and Usage	(b) (4)	LONSURF, as a single agent or in combination with bevacizumab, is indicated for the treatment of adult patients with metastatic colorectal cancer previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.
Section 2: Dosage and Administration		(b) (4)
Section 2: Dosage and Administration		(b) (4)

		bevacizumab.
Section 5: Warnings and Precautions	Severe myelosuppression updated	None
Section 6: Adverse Reactions	Pooled clinical trials experience updated (Section 6.1) Data from SUNLIGHT described	None
Section 8: Use in Specific Populations	Updated information on geriatric use based on SUNLIGHT data	None
Section 14: Clinical Studies	Efficacy results described for SUNLIGHT trial	None

11.2 Patient Labeling

Minor edits to align with USPI.

APPEARS THIS WAY ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

The safe use of FTD/TPI plus bevacizumab can be adequately implemented in the postmarketing setting without issuing a REMS for this combination regimen. The product label for FTD/TPI contains information on common and clinically significant adverse reactions that have been observed with FTD/TPI plus bevacizumab. Product labeling also includes dose modification and management guidelines for these events. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of FTD/TPI plus bevacizumab.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

No PMRs or PMCs were issued for this supplemental NDA.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (OB) Comments

X

Pallavi Mishra-Kalyani

15 Division Director (Clinical) Comments

X

'Lola Fashoyin-Aje

APPEARS THIS WAY ON ORIGINAL

16 Appendices

16.1 References

1. Lonsurf Prescribing Information. Drugs@FDA [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration. [cited 27 Jul 2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf
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16.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): SUNLIGHT Trial

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 719		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in S Sponsor of covered study: Taiho Oncology Inc		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

sNDA 207981/012 Taiho Oncology, Inc.
Lonsurf Prior Approval Supplement – Efficacy

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Geetika Srivastava	Division of Oncology 3	Sections: 2, 3, 7, 8, 9, 10, 12, 13, and 19 Appendices 19.1 and 19.2	**Select one:** _X_ Authored ___ Approved
	Signature: Geetika Srivastava -S Digitally signed by Geetika Srivastava -S Date: 2023.07.12 11:13:07 -04'00'			
Clinical Team Leader	Jamie Brewer	Division of Oncology 3	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: See Signature in DARRTs			
Biostatistics Reviewer	Yi Ren	Division of Biostatistics V	Sections: 8.1, 8.3	**Select one:** _X_ Authored ___ Approved
	Signature: Yi Ren -S Digitally signed by Yi Ren -S Date: 2023.07.12 12:28:10 -04'00'			
Biostatics Team Lead	Anup Amatya	Division of Biostatistics V	Sections: 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature: Anup K. Amatya -S Digitally signed by Anup K. Amatya -S Date: 2023.07.12 12:41:04 -04'00'			
Biostatistics Supervisor	Pallavi Mishra-Kalyani	Division of Biostatistics V	Sections: 8.1, 8.3	**Select one:** _ Authored _X_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2023.07.20 12:27:24 -04'00'			

Associate Director for Labeling (ADL)	Doris Auth	Oncology Center for Excellence	Sections: All	**Select one:** ___Authored __X_Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.07.17 07:14:24 -04'00'			
Cross Discipline Team Lead	Jamie Brewer	Division of Oncology 3	Sections: All	**Select one:** X Authored X_Approved
	Signature: See signature in DARRTs			
Division Director (Clinical)	Lola Fashoyin-Aje	Division of Oncology 3	Sections: All	**Select one:** X_Approved
	Signature: See signature in DARRTs			

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207981Orig1s012

OTHER REVIEW(S)

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

PATIENT LABELING REVIEW

Date:	July 7, 2023
To:	Gina Davis, MT Senior Regulatory Health Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD, BCACP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LONSURF (trifluridine and tipiracil)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 207981
Supplement Number:	S-012
Applicant:	Taiho Oncology, Inc.

1 INTRODUCTION

On February 13, 2023, Taiho Oncology, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved New Drug Application (NDA) 207981/S-012 for LONSURF (trifluridine and tipiracil) tablets. With this supplement, the Applicant is seeking to extend the use of LONSURF to include the combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatine-, and irinotecan-based chemotherapy, and anti-VEGF bilogoical therapy, and if RAS wil-type, an anti-EGFR therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on April 3, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LONSURF (trifluridine and tipiracil) tablets.

2 MATERIAL REVIEWED

- Draft LONSURF (trifluridine and tipiracil) tablets PPI received on February 13, 2023, and accessed from the SharePoint Link provided by DO3 by DMPP and OPDP on July 5, 2023.
- Draft LONSURF (trifluridine and tipiracil) tablets Prescribing Information (PI) received on February 13, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 5, 2023.
- Approved LONSURF (trifluridine and tipiracil) tablets labeling dated January 1, 2020.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we:

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

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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07/07/2023 11:44:58 AM

LASHAWN M GRIFFITHS
07/10/2023 10:26:36 AM

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

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

Memorandum

Date: July 07, 2023

To: Gina Davis, MT, Regulatory Project Manager, Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, DO3

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for LONSURF (trifluridine and tipiracil) tablets, for oral use

NDA: 207981, S-012

Background: In response to DO3's consult request dated April 3, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement-012 for LONSURF (trifluridine and tipiracil) tablets, for oral use (Lonsurf). This supplement proposes a new indication, in combination with bevacizumab, for the treatment of previously treated adult patients with metastatic colorectal cancer.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on July 5, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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