# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 207981Orig1s000

# OFFICE DIRECTOR MEMO

# Office Director Summary Review for Regulatory Action

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|---|---|
| **Date** | Electronic stamp date |
| **From** | Richard Pazdur |
| **Subject** | Office Director Summary Review |
| **NDA #** | NDA 207981 |
| **Applicant Name** | Taiho |
| **Date of Submission** | December 19, 2014 |
| **PDUFA Goal Date** | December 18, 2015 |
| **Proprietary Name / Established (USAN) Name** | Lonsurf/ trifluridine/tipiracil |
| **Dosage Forms / Strength** | Tablets for oral use/ 15mg and 20mg |
| **Proposed Indication(s)** | "for the treatment of patients with metastatic colorectal cancer who have been previously treated with, (b) (4) fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy" |
| **Recommended Action for NME** | *Approval* |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Division Director | Patricia Keegan |
| Regulatory Project Manager Review | Gina Davis |
| Medical Officer Review | Leigh Marcus |
| Statistical Review | Weishi (Vivian) Yuan |
| Nonclinical Pharmacology/Toxicology Review | G. Sachia Khasar & Emily M. Fox |
| Quality Review | Erika Englund & Rajiv Agarwal; |
| Microbiology Review | Quamrul Majumder & Marisa Heayn |
| Biopharmaceutics Review | Salaheldin Hamed |
| Clinical Pharmacology/Pharmacometrics Review | Xianhua (Walt) Cao & Jingyu (Jerry) Yu |
| OSI Review | Lauren Iacono-Connors |
| CDTL Review | Steven Lemery |
| OPDP Consult Review | Carole Broadnax |
| OSE/DMEPA Consult Review | Otto Townsend |
| OSE/DRISK Consult Review | Mona Patel |
| DPMH Consult review | Ethan Hausman |
| Patient Labeling Team review | Morgan Walker |

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH= Division of Pediatric and Maternal Health

## 1. Introduction

On December 19, 2014, Taiho Pharmaceuticals submitted an NDA for Lonsurf (trifluridine/tipiracil), which is a new molecular entity consisting of trifluorithymidine (FTD; trifluridine) and tipiracil (TPI). Trifluridine is a thymidine-based nucleoside analog, which can be incorporated into deoxyribonucleic acid (DNA) following phosphorylation and inhibit cell proliferation. Tipiracil is a thymidine phosphorylase inhibitor, which contributes to the action of Lonsurf by inhibiting degradation of trifluridine, leading to increased systemic exposure to trifluridine. Trifluridine was approved on April 10, 1980 (NDA 18299 for Viroptic) for the treatment of primary kerato-conjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2."

The major issue considered in this application was whether this single randomized trial provided substantial evidence of effectiveness and whether the risk:benefit ratio was favorable. The demonstration of a modest but clinically important improvement in overall survival and progression-free survival was statistically robust. The adverse reaction profile is similar to drugs which patients would have already received as part of their prior treatment. The incidence and severity of the gastrointestinal and myelosuppressive toxicity observed in this study would be considered acceptable in light of the benefits and is supported by the relatively low incidence of dose reductions (13.7%) and 3.6% discontinuation rate for an adverse reaction. I concur with the review team members that this application should be approved.

## 2. Background

Based on SEER data, there will be an estimated 132,700 new cases of colorectal cancer and 49,700 deaths due to colorectal cancer in 2015.[1] Approximately 20% of colorectal cancers have distant metastases disease at diagnosis and the 5-year survival rate for those with metastatic disease is 13%.

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

Available therapy for this population is limited to one FDA-approved drug, Stivarga (regorafenib), which was approved on September 27, 2012, for "the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy." This approval was based on demonstration of a single, randomized, multicenter, placebo-controlled clinical trial (CORRECT trial) comparing regorafenib to a matching placebo. The CORRECT trial demonstrated statistically significant improvements in both overall survival [HR =0.77 (0.64, 0.94)] with KM-estimated median survival times 6.4 and 5.0 months and in progression-free survival [HR = 0.49 (0.42, 0.58)] with estimated median PFS of 2.0 and 1.7 months, in the regorafenib and placebo arms, respectively. The overall response rates were similar between arms (1% vs. 0.4%).

Based on the proposed indication, other drugs approved for the treatment of metastatic colorectal cancer cannot be approved available therapy due to the requirement to have prior receipt of, or intolerance to, such therapy.

## 3. CMC

There are no issues that preclude approval from a CMC perspective. CMC has provided an overall acceptability of the manufacturing of the drug product and drug substance. Lonsurf will be marketed as film-coated immediate release tablets for oral administration in two strengths: a white "15 mg" tablet containing 15 mg trifluridine and 6.14 mg tipiracil and a pale red "20 mg" tablet containing 20 mg trifluridine and 8.19 mg tipiracil. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months.

[1] http://seer.cancer.gov/statfacts/html/colorect.html. Accessed on September 19, 2015.

## 4. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval from a nonclinical perspective. The NDA contained the results of in vitro and in vivo studies assessing the pharmacodynamic effects of trifluridine and of tipiracil, individually. Concomitant administration of tipiracil and trifluridine resulted in increases in trifluridine exposure of ≥ 100-fold as compared to trifluridine alone in non-human primates chronic (13-week) toxicology studies. Tipiracil, as a single agent, did not inhibit tumor growth in tumor xenograft models.

In chronic toxicology studies in rats and monkeys, the major target organs were the hematopoietic system and gastrointestinal (GI) tract. Safety pharmacology studies indicate that trifluridine/tipiracil does not have significant effects on the neurologic, cardiovascular, or respiratory systems. Trifluridine/tipiracil crossed the placenta and was detectable in breast milk in rats. Trifluridine/tipiracil was embryotoxic and teratogenic when at exposures comparable to that achieved with the recommended human dose administered early in gestation, but did not alter fertility in female rates. In vitro studies indicate that trifluridine is genotoxic.

## 5. Clinical Pharmacology/Pharmacometrics

There are no clinical pharmacology issues that preclude approval. The pharmacokinetics (PK) of trifluoridine/tipiracil were characterized, demonstrating that systemic exposure (AUC) of trifluridine increased more than dose proportionally over the dose range of 15 to 35 mg/m$^2$. The mean elimination half-life of trifluridine at steady state was 2.1 hours and of tipiracil was 2.4 hours. Study results supported the specific labeling recommendation that TAS-102 be administered under fed conditions (*e.g.*, within 1 hour after completion of morning and evening meals). In addition, no dose adjustments are required when Lonsurf is administered with concomitant medications because neither trifluridine nor tipiracil are metabolized by cytochrome P450 (CYP) enzymes and concomitant administration of OCT2 inhibitor had no clinically meaningful effect on exposure to trifluridine or tipiracil.

A population PK (PopPK) analyses that included data from 239 patients who received the proposed dosage regimen identified that body size and renal function are the primary intrinsic factors affecting the exposure to trifluridine and tipiracil. Based on the PopPK analysis, the proposed adjustment for the dose by body surface area (BSA) was determined to be appropriate and supported the labeling recommendation that dose adjustment is required for patients with mild hepatic impairment, and mild to moderate renal impairment.

The exploratory exposure-response (E-R) analyses were inconclusive data from only 138 Lonsurf-treated patients enrolled in Study TAS-102-301 trial were included in these analyses and the survival in this subgroup appeared better than in the ITT population, suggesting that this subgroup might not be representative of the overall population. In E-R analyses, the 138 patients were divided evenly into a “high trifluridine AUC” and a “low trifluridine AUC” subgroup. There was a suggestion that survival was longer and the incidences of Grade ≥3 neutropenia and of all Grade ≥3 drug related adverse events were higher in the subgroup of patients with “high trifluridine AUC” than in those with “low trifluridine AUC”.

An ECG substudy was incorporated into Study TAS-102-301 to assess effects on cardiac electrophysiology. Based on the results of this study, given the absence of clinically significant effects in the hERG assay or in a nonclinical safety cardiology study, the QT-IRT consultant concluded that trifluridine/tipiracil is unlikely to cause clinically relevant QT prolongation.

## 6. Clinical Microbiology

There are no clinical microbiology or sterility issues that preclude approval.

## 7. Clinical/Statistical-Efficacy

This NDA relied primarily on the results of a single multicenter, randomized (2:1), double-blind, placebo-controlled trial, Study TPU-TAS-102-301 (RECOURSE). Key eligibility criteria were histologically documented metastatic colorectal cancer (mCRC); prior treatment with at least two chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF-directed biologic, and an anti-EGFR therapy if *KRAS* wild-type mCRC, or evidence of intolerance to one or more such agents; ECOG PS 0-1; absence of CNS metastases; and absence of ascites requiring drainage. Patients were randomized to trifluridine/tipiracil or placebo (2:1); 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). Patients were randomized to receive trifluridine/tipiracil at a dose of 35 mg/m$^2$ based on the trifluridine component or matching placebo administered orally twice daily after meals on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS) and key secondary efficacy endpoints were progression-free survival (PFS) and overall response rate (ORR).

A total of 800 patients were enrolled and randomized; 534 patients were randomized to trifluridine/tipiracil and 266 patients were randomized to placebo. The median age was 63 years, 61% were male, 58% and 35% were White and Asian respectively, and all patients had baseline ECOG PPS 0 or 1. The primary site of disease was colon (62%) or rectum (38%). All patients had received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and all but one patient received prior bevacizumab. Approximately half (49%) of the study population had KRAS wild-type mCRC; all but two patients with KRAS wild-type mCRC received panitumumab or cetuximab.

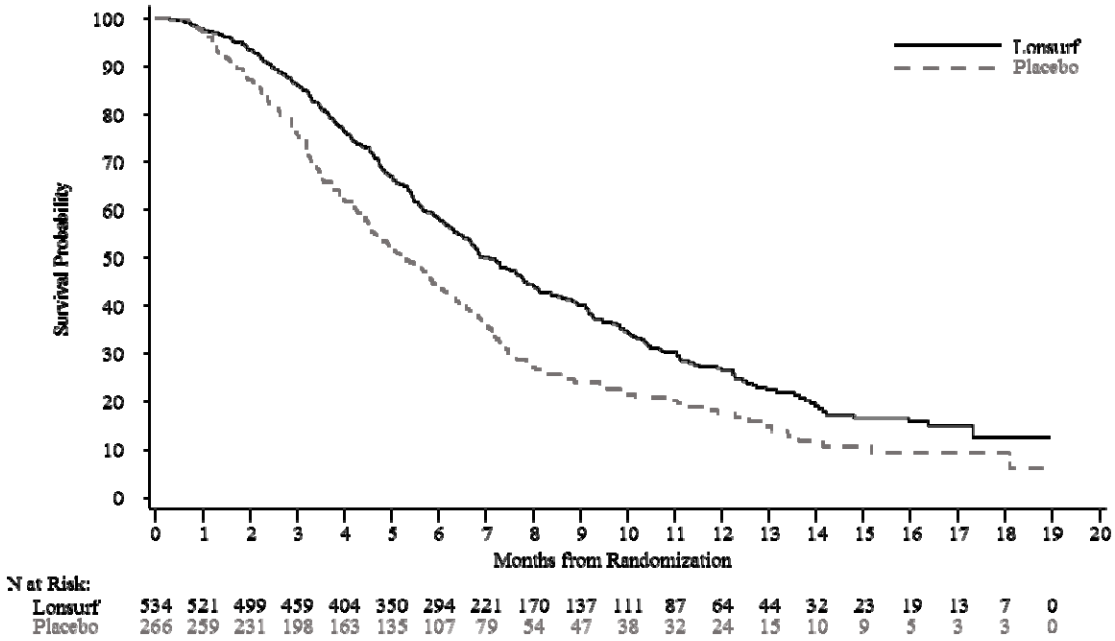
Study TAS-102-301 demonstrated a clinically important and statistically significant improvement in OS [hazard ratio (HR) 0.68 (95% confidence interval (CI): 0.58, 0.81); p<0.001] with median survival times of 7.1 months in the trifluridine/tipiracil arm compared to 5.3 months in the placebo arm. In addition, PFS was also significantly prolonged in the trifluridine/tipiracil arm as compared to placebo [HR 0.47 (95% CI: 0.40, 0.55); p<0.001].

Table 1 Efficacy Results

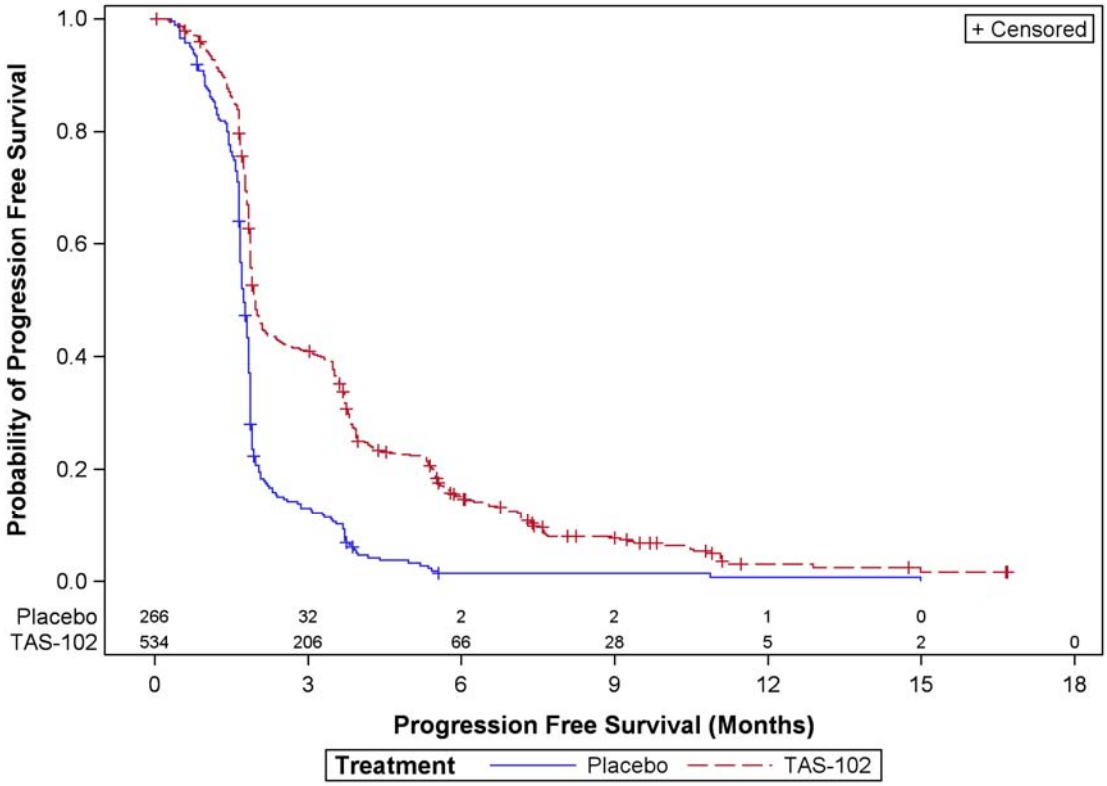
| | trifluridine/tipiracil (N=534) | placebo (N=266) |
|---|---|---|
| **Overall Survival** | | |
| Number of deaths, N (%) | 364 (68) | 210 (79) |
| Median OS (months)[a] [95% CI][b] | 7.1 [6.5, 7.8] | 5.3 [4.6, 6.0] |
| Hazard ratio [95% CI] | 0.68 [0.58, 0.81] | |
| P-value[c] | <0.001 | |
| **Progression-Free Survival** | | |
| Number of Progression or Death, 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)

K-M Curves of Overall Survival




K-M Curves of Progression-free Survival



## 8. Safety

There were 533 patients treated with trifluridine/tipiracil in Study-102-301, which is sufficient to detect adverse reactions occurring at an incidence of approximately 1%. The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with trifluridine/tipiracil 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. However the incidence of Grade 3 or 4 adverse events, with the exception of myelosuppression, was low with 7% Grade 3-4 asthenia/fatigue and 4% Grade 3-4 decreased appetite, 3% Grade 3-4 diarrhea, and other Grade 3-4 adverse reactions occurring at an incidence of 2% or less.

The most serious safety concerns identified for trifluridine/tipiracil were severe myelosuppression, with 0.2% fatality due to neutropenic sepsis and an incidence of Grade 3-4 neutropenia of 38%, Grade 3-4 anemia of 18%, Grade 3-4 thrombocytopenia of 5% and incidence of febrile neutropenia of 3.8%. Across Study 102-301, 9.4% of patients receiving trifluridine/tipiracile required granulocyte-colony stimulating factors. In Study 102-301, 3.6% of patients discontinued trifluridine/tipiracil for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

## 9. Advisory Committee Meeting

This new molecular entity was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with unresectable advanced or recurrent colorectal cancer. The application did not raise significant public health questions on the role of Lonsurf for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from an advisory committee discussion.

## 10. Pediatrics

A full waiver of PREA requirements is granted because pediatric studies are impossible or highly impractical as colorectal cancer because the number of pediatric patients with colorectal cancer is so small.

## 11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment
  Metastatic colorectal cancer is a serious and life-threatening disease with a 5-year survival rate of 16% from diagnosis of metastatic disease. In the major efficacy trial, the median survival in the control arm was 5.1 months.

  This single multicenter, randomized, double-blind, placebo-controlled trial, enrolling 800 patients demonstrated a clinically important and statistically significant improvement in OS [HR 0.68 (95% CI: 0.58, 0.81); p<0.001] with median survival times of 7.1 months in the trifluridine/tipiracil arm compared to 5.3 months in the placebo arm. In addition, PFS was also significantly prolonged in the trifluridine/tipiracil arm as compared to placebo [HR 0.47 (95% CI: 0.40, 0.55); p<0.001]. The adverse reaction profile of trifluridine/tipiracil is similar to drugs which patients would have already received as part of their prior treatment. The most common adverse reactions of this combination drug were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia. However, the incidence of Grade 3 or 4 adverse events, with the exception of myelosuppression, was low with 7% Grade 3-4 asthenia/fatigue and 4% Grade 3-4 decreased appetite, 3% Grade 3-4 diarrhea, and other Grade 3-4 adverse reactions occurring at an incidence of 2% or less. The most serious safety concerns identified for trifluridine/tipiracil were severe myelosuppression, with 0.2% fatality due to neutropenic sepsis and an incidence of Grade 3-4 neutropenia of 38%, Grade 3-4 anemia of 18%, Grade 3-4 thrombocytopenia of 5%)

and incidence of febrile neutropenia of 3.8%. Across Study 102-301, 9.4% of patients receiving trifluridine/tipiracile required granulocyte-colony stimulating factors.

This patient population has only one effective, alternative therapy (regorafenib) which provides and improvement in survival of a similar magnitude. Therefore, there is a continued unmet need for effective treatments, where patients may choose treatment based on the adverse reaction profile or in light of other co-morbid conditions. The incidence and severity of the gastrointestinal and myelosuppressive toxicity observed in this study would be considered acceptable by the oncology community and patients in light of the benefits. The tolerability of this agent is supported by the relatively low incidence of dose reductions (13.7%) and 3.6% discontinuation rate for an adverse reaction.

The Risk benefit profile, which was also discussed by Drs. Keegan, Lemery and Marcus is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Postmarketing Requirements and Commitments
  See action letter.

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/s/

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TAMY E KIM
09/22/2015

RICHARD PAZDUR
09/22/2015