2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Taiho Oncology, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Lonsurf®</td></tr>
<tr><td>Name of Active Ingredient:
TAS-102 (trifluridine/tipiracil hydrochloride)</td></tr>
<tr><td colspan="3">Title of Study: Randomized, Double-Blind, Phase 3 Study Evaluating TAS-102 Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Gastric Cancer Refractory to Standard Treatments</td></tr>
<tr><td colspan="3">Principal Investigators:
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<tr><td colspan="3">Study centers: 110 centers in 17 countries: Italy (14), United States (12), Turkey (11), France (9), Japan (9), Portugal (9), United Kingdom (7), Israel (6), Spain (6), Russian Federation (5), Germany (4), Poland (4), Czech Republic (4), Belgium (3), Ireland (3), Belarus (3), and Romania (1).</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient randomized: 24 February 2016
Date last patient randomized: 05 January 2018
Data cut-off dates: 31 March 2018 (non-survival data)
30 April 2018 (overall survival data)</td><td>Phase of development: 3</td></tr>
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Objectives:

Primary:

- Overall survival (OS)

Key Secondary:

- Progression-free survival (PFS) based on Investigator assessment of radiologic images
- Safety and tolerability

Other Secondary:

- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to deterioration of Eastern Cooperative Oncology (ECOG) performance status to score of 2 or higher
- Quality of Life (QoL) as evaluated by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the QLQ-STO22, which is a module specific to patients with gastric cancer

Methodology:

This was a multinational, double-blind, 2-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who received at least 2 prior regimens for advanced disease. Eligible patients were centrally randomized (2:1) to TAS-102 plus BSC (experimental arm) or placebo plus BSC (control arm). Randomization was stratified by: region (Japan vs ROW1 [European Union, United States]); ECOG performance status (0 vs 1); and prior treatment with ramucirumab (yes vs no).

Computed tomography scans were performed at baseline and every 8 weeks thereafter until disease progression. On-site tumor assessments were performed by the Investigator/local radiologist using Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1, 2009). Patients who discontinued for reasons other than radiologic disease progression (ie, intolerable side effects), were followed every 8 weeks for tumor response until radiologic disease progression or initiation of new anticancer therapy (whichever occurred first).

Quality of Life was evaluated using the EORTC QLQ-C30 and the QLQ-STO22 questionnaires.

Safety assessments included recording of adverse events from the first dose of study treatment (or worsened after the start of treatment) through 30 days after the last dose of study treatment and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Safety assessments also included evaluation of laboratory test results, vital signs measurements, physical examination findings, and changes in ECOG performance status score.

Number of patients (planned and analyzed): A total of 500 patients were planned to be enrolled and 507 patients were randomized in a 2:1 ratio to TAS-102 plus BSC or placebo plus BSC (337 to TAS-102 plus BSC; 170 to placebo plus BSC). The analysis populations were as follows:

Table 1: Analysis Populations by Treatment Group

	Number (%) of Patients		
	TAS-102 n (%)	**Placebo n (%)**	**Total n (%)**
Intent-to-treat (ITT)	337 (100)	170 (100)	507 (100)
As-treated (AT)	335 (99.4)	168 (98.8)	503 (99.2)
Tumor response (TR)	290 (86.1)	145 (85.3)	435 (85.8)

Source: Table 14.1.1.1, Table 14.1.1.3

Diagnosis and main criteria for inclusion:

Key inclusion and exclusion criteria are listed below. A complete list of inclusion and exclusion criteria is provided in Section 9.3. Patients must have met all of the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

Key inclusion criteria:

1. Provided written informed consent.
2. Had histologically confirmed, documented, non-resectable, metastatic gastric adenocarcinoma including adenocarcinoma of the gastroesophageal junction as defined by the American Joint Committee on Cancer staging classification (7th ed., 2010).
3. Previously received at least 2 prior regimens (at least 1 cycle per regimen) for advanced disease and were refractory to or unable to tolerate their most recent prior therapy:
   a. Prior regimen(s) must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumors are human epidermal growth factor receptor 2-neu-positive (HER2+) must have received prior anti-HER2+ therapy if available.
   b. Patients had progressed based on imaging during or within 3 months of the last administration of their most recent prior regimen.
   c. Patients who had withdrawn from their most recent prior regimen due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease were also eligible to enter the study.
   d. Patients who received postoperative adjuvant chemotherapy or chemo-radiotherapy, and had recurrence during or within 6 months of completion of the adjuvant chemotherapy were allowed to count the adjuvant therapy as 1 prior regimen for advanced disease.
4. Had measurable or non-measurable disease as defined by RECIST 1.1 criteria.
5. Had an ECOG performance status of 0 or 1 at time of randomization.
6. Had adequate organ function based on laboratory test results.

Key exclusion criteria:

1. Had a serious illness or medical condition(s) as detailed in Section 9.3.2.
2. Had any of the following within the specified time frame prior to randomization: major surgery, extended field radiation, or any investigational drug/device within prior 4 weeks; any anticancer therapy within prior 3 weeks; or limited field radiation within prior 2 weeks.
3. Had previously received TAS-102 or had hypersensitivity to TAS-102 or any of its ingredients.
4. Had unresolved toxicity of greater than or equal to CTCAE Grade 2 attributed to any prior therapies (excluding anemia, alopecia, skin pigmentation, and platinum-induced neurotoxicity).

Test product, dose and mode of administration, batch number:

TAS-102 is an immediate-release film-coated tablet, supplied in 2 strengths: 15 mg white, round tablet (15 mg trifluridine [FTD]/7.065 mg tipiracil hydrochloride [TPI]) and 20 mg pale-red, round tablet (20 mg FTD/9.42 mg TPI). Batch numbers of TAS-102 are provided in an appendix.

TAS-102 (35 mg/m^2/dose) was administered orally twice daily (BID), within 1 hour after completion of morning and evening meals, for 5 days each week with 2 days rest for 2 weeks, followed by a 14-day rest, repeated every 4 weeks.

Reference therapy, dose and mode of administration, batch number:

Placebo tablets identical in appearance to the TAS-102 15-mg (white, round) and 20-mg (pale-red, round) tablets. Batch numbers are provided in an appendix. Placebo was administered as described above for TAS-102. Batch numbers are provided in an appendix.

Duration of treatment: Patients received blinded study treatment until a discontinuation criterion was met or until completion of the primary endpoint analysis, whichever was sooner.

Criteria for evaluation:

Efficacy:

Tumor assessments were analyzed using RECIST (version 1.1, 2009).

Quality of Life was evaluated using the EORTC QLQ-C30 and the QLQ-STO22 questionnaires.

Safety:

Standard safety monitoring was performed and adverse events were graded using NCI CTCAE version 4.03.

Statistical methods:

Sample size determination:

The study was designed to detect with 90% power a hazard ratio (HR) for death of 0.70 (30% risk reduction) in the TAS-102 group compared with the placebo group with an overall 1-sided type 1 error of 0.025. A variable accrual period of 18 months and a 5%/year loss to survival follow-up rate was assumed. Using a treatment allocation of 2:1 (TAS-102:placebo) of 500 patients, 384 deaths were targeted for the final OS analysis.

Analysis populations:

- The ITT population: Includes all randomized patients, regardless of whether or not study treatment was administered, and is the primary analysis population for all efficacy parameters. All analyses using this population were based on the treatment assigned by the Interactive Voice/Web Response System (IXRS).
- The AT population: Includes all patients who received at least 1 dose of study treatment. This population was used for safety analyses. All analyses using this population were based on the treatment actually received.
- The tumor response (TR)-evaluable population: Includes all patients in the ITT population who had measurable disease (at least 1 target lesion) at baseline and had at least 1 post-baseline evaluation or early disease progression/cancer-related death occurred before the first evaluation while on treatment. All analyses for this population were based on the IXRS treatment assigned.

Primary endpoint: Overall survival was defined as the time from the date of randomization to the date of death. If death was not observed during the study, the time was censored at the last date the patient is known to be alive or the cut-off date, whichever occurred earlier. For the primary analysis of OS, the 2 treatment groups were compared using the stratified log-rank test using the 3 stratification factors. The HR was estimated, along with the associated 2-sided 95% confidence intervals (CI), using a stratified Cox's proportional hazard model. Survival for each treatment group was summarized using Kaplan-Meier curves and further characterized in terms of the median and survival probability at 3, 6, 9 and 12 months, along with the corresponding 2-sided 95% CI for the estimates.

Key secondary efficacy endpoint: Progression-free survival was evaluated from the date of randomization to the first occurrence of radiologic progression or death. Treatment comparisons for PFS used similar analytical methods as the OS endpoint.

Other efficacy endpoints: Overall response rate and DCR were compared between the treatment groups using Fisher's exact test; associated 95% CIs were also derived. Time to deterioration of ECOG performance status to a score of ≥ 2 was analyzed as described for PFS. Changes in QoL scores from baseline to each cycle were determined for the summary, all domains, and single items.

Safety endpoints: Comprehensive safety analyses were based on the AT population. Simple descriptive statistics were provided for safety endpoints and demographic/baseline characteristics.

Interim analysis: The interim analysis was performed based on 220 events (deaths) reported as of 31 Aug 2017. The associated efficacy boundary suggested to the Data Monitoring Committee was 1-sided p-value of 0.0031, and the associated futility boundary was OS HR ≥ 0.95. The observed HR, based on 200 events, was 0.7321 with 95% CI (0.5540, 0.9676) and 1-sided p-value 0.0138. The associated median OS was 5.7 months for the TAS-102 group and 3.8 months for the placebo group. An additional sensitivity analysis was presented based on all events (deaths) reported as of the date of the 192nd death (194 deaths were reported as of that date) and the corresponding efficacy boundary for the sensitivity analysis was 1-sided p-value of 0.0016. Considering the alpha-spending that took place for the interim analysis, the associated efficacy boundary for the final analysis (assuming 384 events as planned) is 1-sided p-value of 0.0215.

SUMMARY

Disposition of patients and demographic characteristics:

A total of 625 patients signed informed consent for participation in the study. Of these, 118 were screened but not randomized, mainly due to screen failures. Of the 507 patients randomized (ITT population), 337 were assigned to TAS-102 and 170 were assigned to placebo. Two patients in each treatment group did not receive study treatment. Of the 503 patients in the AT population, 481 (95.6%) patients discontinued study treatment, primarily due to clinical progression (TAS-102: 16.1%; placebo: 20.8%) or radiological progression (TAS-102: 57.3%; placebo: 65.5%). Adverse events resulted in

discontinuation from treatment for 9.9% in the TAS-102 group (6.5% for placebo). In the TAS-102 and placebo groups, respectively, 76.7% and 84.5% of patients discontinued from the study. In the AT population, 19 (5.7%) patients in the TAS-102 group and 3 (1.8%) in the placebo group were still receiving treatment as of the clinical data cut-off (31 Mar 2018).

The median age in the ITT population was 63.0 years (range: 24 to 89 years), with 45.0% ≥ 65 years and 13.6% ≥ 75 years. The racial composition was primarily White (70.4%) and Asian (15.8%). Male patients comprised 74.8% of the TAS-102 group and 68.8% in the placebo group. Regional distribution included patients from Japan (14.4%), the USA (5.1%), and the other countries hereafter referred to as the EU (80.5%).

Most patients' primary cancer was gastric (71.0%); 28.6% of patients had gastroesophageal junction cancer and 0.4% had both types. The median time from initial diagnosis to randomization was 20.7 months, and the median time from confirmed metastasis to randomization was 15.8 months. Approximately 90% of all patients had measurable disease at baseline. The number of prior treatment regimens received was consistent between treatment groups: 37.5% of patients received 2 prior therapies, 38.3% received 3 prior therapies, and 24.3% received ≥ 4 prior therapies.

EFFICACY RESULTS:

Primary Endpoint – Overall Survival

This study met its primary endpoint and improved survival by 31%, which is clinically meaningful and statistically significant. The addition of TAS-102 to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC (Table 2). The treatment groups were similar with respect to treatments received during follow-up after discontinuation of study treatment including post-treatment use of ramucirumab; therefore, this was not a confounding factor with respect to OS results. The benefit of improved OS was robust and observed consistently for TAS-102 across all randomization strata and 47 of 49 pre-specified subgroups.

Table 2: Overall Survival by Treatment Group (Intent-to-Treat Population)

	TAS-102 (N=337)	**Placebo (N=170)**
Survival (months)[a]		
Q1 (95% CI)[b]	2.9 (2.4, 3.2)	2.1 (1.7, 2.3)
Median (95% CI)	5.7 (4.8, 6.2)	3.6 (3.1, 4.1)
Q3 (95% CI)[b]	10.4 (9.0, 12.4)	8.7 (6.3, 9.9)
p-value (1-sided)[c]	0.0003	
p-value (2-sided)[c]	0.0006	
Hazard ratio TAS-102:placebo (95% CI)	0.6917 (0.5597, 0.8548)	
Number of patients by censoring status, n (%)		
Total patients	337	170
Not censored (dead)	244 (72.4)	140 (82.4)
Censored	93 (27.6)	30 (17.6)
Patients survived by Kaplan-Meier estimates[d] (n, %)		
3 months: n (%) [95% CI]	240 (72.4) [67.3, 76.9]	101 (60.3) [52.4, 67.2]
6 months: n (%) [95% CI]	124 (46.7) [41.1, 52.2]	47 (33.1) [25.9, 40.3]
9 months: n (%) [95% CI]	66 (30.3) [24.9, 35.8]	29 (23.3) [16.8, 30.3]
12 months: n (%) [95% CI]	31 (21.2) [16.1, 26.7]	10 (13.0) [7.7, 19.8]

Source: Table 14.2.1

[a] Kaplan-Meier estimates

[b] Q1, Q3 (25^{th} and 75^{th} percentiles, correspondingly)

[c] Stratified log-rank test (IXRS stratification factors: region, ECOG status at baseline, prior treatment with ramucirumab)

[d] Log-log transformation methodology of Kalbfleisch and Prentice was used.

Key secondary endpoint – PFS

The addition of TAS-102 to BSC also resulted in a statistically significant improvement in the key secondary endpoint, PFS, compared to placebo plus BSC, with HR of 0.57 and 1-sided and 2-sided $p<0.0001$ (stratified log-rank test). The median PFS was 2.0 months for the TAS-102 group versus 1.8 months for the placebo group. The percentage of patients progression free was consistently higher for the TAS-102 group than for the placebo group, starting at the time of the initial post baseline tumor assessment at 2 months (TAS-102: 49.7%; placebo: 25.3%). The benefit of increased PFS was consistent for TAS-102 across all randomization strata and pre-specified subgroups.

Other Secondary Endpoints

- For the TR population, ORR (CR + PR) was 4.5% for the TAS-102 group (1 CR and 12 PR) and 2.1% (3 PR) in the placebo group. A statistically significant difference in DCR (29.7%) was observed between the TAS-102 and placebo groups (44.1% and 14.5%, respectively; 95% CI: 21.6, 37.7; $p<0.0001$).
- The median time to deterioration of ECOG performance status to ≥ 2 was 4.3 months for the TAS-102 group versus 2.3 months for the placebo group (HR: 0.69) and the difference was statistically significant ($p = 0.0005$).
- Overall, for the treatment period, QoL remained stable in both treatment groups with no clinically relevant changes from baseline, indicating that QoL was maintained during treatment with TAS-102. No statistically significant differences in the time to deterioration of QoL scores between TAS-102 and placebo groups have been observed.

SAFETY RESULTS:

Extent of exposure:

As of the cut-off date, the mean (median) exposure was 12.1 (6.7) weeks in the TAS-102 group and 7.1 (5.7) weeks in the placebo group. The median number of cycles initiated was 2.0 for both groups. The median relative dose intensities in the TAS-102 group (0.90) and in the placebo group (0.95) indicate high compliance with the dosing schedule in both groups.

Adverse events

The overall incidence of adverse events was 97.3% for the TAS-102 group and 93.5% for the placebo group. The incidence of treatment-related (as assessed by the investigator) adverse events was higher in the TAS-102 group than in the placebo group (80.9% vs 56.6%), including the incidences of Grade ≥ 3 adverse events (79.7% vs 57.7%), and treatment-related serious adverse events (11.6% vs 3.6%).

In the TAS-102 group, the most frequently reported adverse events (all grades) were anemia (44.5% vs 19.0% for placebo), neutropenia (38.5% vs 3.6%), nausea (37.0% vs 31.5%), decreased appetite (34.3% vs 31.0%), fatigue (26.6% vs 20.8%), vomiting (24.8% vs 20.2%), and diarrhea (22.7% vs 14.3%). Adverse events occurring at $\geq 10\%$ higher incidence in the TAS-102 group than in the placebo group were anemia, neutropenia, leukopenia, and neutrophil count decreased, which are established adverse events associated with the use of TAS-102. In the TAS-102 group, frequently reported Grade 3 or higher adverse events were neutropenia (23.3% vs 0% for placebo), anemia (18.8% vs 7.7%), and neutrophil count decreased (11.3% vs 0.0%). In the TAS-102 group, the most frequently reported treatment-related adverse events were neutropenia (37.6% vs 3.6% for placebo), anemia (31.0% vs 8.9%), and nausea (25.4% vs 15.5%).

The incidence of serious adverse events was similar for the TAS-102 (42.7%) and placebo groups (41.7%); treatment-related serious adverse events were experienced by 11.6% and 3.6%, respectively. The percentage of patients with adverse events leading to treatment discontinuation was 12.8% in the TAS-102 group and 16.7% in the placebo group.

Deaths

As of the cut-off data for non-survival data (31 Mar 2018), a total of 104 patients died while on treatment or within 30 days after last dose; the majority of on-study deaths in both groups were due to disease progression. Forty-five (13.4%) patients in the TAS-102 group and 19 (11.3%) patients in the placebo group experienced adverse events resulting in death. The most frequently reported adverse event resulting in death in both treatment groups was general physical health deterioration. One fatal adverse event in each treatment group was considered related to study treatment.

In total, 17 deaths occurred on study or within 30 days after last dose of study therapy for which an adverse event was identified by the investigator as the primary cause of death (15 patients in the TAS-102 group [including 1 patient whose cause of death was "Other"] and 2 patients in the placebo group). For the 15 fatal serious adverse events for patients in the TAS-102 group, 11 were due disease progression and 4 were due to Grade 5 adverse events. Fourteen of the 15 fatal serious adverse events were assessed by the investigator as not related to TAS-102.

Adverse Events of Special Interest

Hematologic impairment-related adverse events were experienced by 71.3% of patients in the TAS-102 group and 24.4% in the placebo group; 49.6% and 9.5%, respectively, had Grade 3 or higher events. Gastrointestinal-related adverse events (diarrhea and/or nausea and/or vomiting) were reported for 54.9% of patients in the TAS-102 group and 45.8% in the placebo group; 7.2% and 6.0%, respectively, had Grade 3 or higher events. Hematological and gastrointestinal adverse events are established adverse events associated with the use of TAS-102.

Laboratory Test Results

For hemoglobin, leukocytes, lymphocytes, neutrophils, and platelets, a higher percentage of patients in the TAS-102 group experienced Grade 3 or 4 test results and worsening from baseline of ≥ 2 toxicity grades than in the placebo group. In the TAS-102 group, $\leq 2.5\%$ of patients had Grade 4 results for all hematology parameters except neutrophil count decreases. Grade 3 and 4 results, respectively, for neutrophil count decreases were reported for 26.8% and 11.3% in the TAS-102 group and 0% in the placebo group.

The incidence of febrile neutropenia (preferred terms) was 1.8% in the TAS 102 group (0% in the placebo group). All febrile neutropenia events were considered treatment-related and Grade 3 or 4 in severity. Although febrile neutropenia led to dose modifications for some of these patients, none led to treatment discontinuation, and all events resolved.

Other safety parameters

No clinically relevant changes in body weight or vital signs were observed in either treatment group. For ECOG performance status, 23.6% patients in the TAS-102 group and 33.9% in the placebo group had deteriorated from a score of 0 or 1 at baseline to ≥ 2 at the last collection cycle.

CONCLUSION:

Study TAS-102-302 was a multinational, double-blind, two-arm, parallel, randomized, Phase 3 study evaluating the efficacy and safety of TAS-102 plus BSC versus placebo plus BSC in patients with metastatic gastric cancer who received at least 2 prior regimens for advanced disease.

The addition of TAS-102 to BSC resulted in a statistically significant and clinically meaningful improvement in OS compared to placebo plus BSC, demonstrating a 31% reduction in the risk of death in the TAS-102 group. The benefit of improved OS was robust and observed consistently for TAS-102 across all randomization strata (Region 1; ECOG performance status; and prior treatment with ramucirumab). Treatment benefit consistently favored the TAS-102 group, with only 2 exceptions noted of the 49 subgroups examined: patients who did not receive prior taxane therapy (HR=1.14) and patients with well-differentiated tumors (HR=1.20). Both subgroups comprised a small number of patients (n=48 and 46, respectively), each accounting for less than 10% of the population. In both cases, corresponding PFS results clearly favored the TAS-102 group. Multivariate analysis did not identify

prior taxane use as a prognostic or predictive factor; while histology subtype showed some prognostic value, it did not demonstrate any predictive effect.

The addition of TAS-102 to BSC demonstrated a statistically significant improvement over placebo plus BSC in PFS across all stratification factors and trended favorably for all subgroups examined. Across all prespecified subgroups, the results consistently support the OS.

The DCR was statistically significantly higher for the TAS-102 group compared to the placebo group, although the difference in ORR between treatment groups was not statistically significant.

A statistically significant prolongation of ECOG performance status ≥ 2 was observed for the TAS-102 group compared to the placebo group.

Overall, QoL remained stable in both treatment groups with no clinically relevant changes from baseline.

Adverse events associated with the use of TAS-102 were generally manageable and consistent with the known safety profile of the compound. The most frequently observed adverse events were hematological and gastrointestinal in nature, which are established adverse events of TAS-102.

The demonstrated efficacy and safety of TAS-102 indicates a favorable benefit/risk ratio for use of TAS-102 in the treatment of patients with metastatic gastric cancer who have failed 2 previous treatments with standard chemotherapeutic regimens.

Date of the initial report: 30 July 2018

Amendment 1: 28 September 2018