2. SYNOPSIS

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Name of Finished Product: S95005 or TAS-102		
Name of Active Ingredient: Trifluridine (FTD) and tipiracil hydrochloride (TPI)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: 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) Protocol No.: CL3-95005-007 EudraCT No.: 2020-001976-14 ClinicalTrials.gov: NCT04737187 Investigational New Drug No: 57674 Universal Trial Number: Not applicable Since the release of the main clinical study report (CSR), there was no global substantial amendment to the protocol.		
International Coordinator [redacted]		
Study countries: A total of 492 patients were randomised in 13 countries as follows: Spain (115 patients), Russian federation (77 patients), Brazil (63 patients), Hungary (47 patients), Italy (39 patients), Poland (34 patients), France (28 patients), Ukraine (21 patients), Denmark (20 patients), United States of America (16 patients), Austria (15 patients), Germany (10 patients), Belgium (7 patients).		
Publication (reference): Prager *et al*., Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 2023; 388:1657-1667.		
Studied period: Initiation date: 25 November 2020 (first visit of first patient) Last randomised patient: 18 February 2022 Primary completion date: 19 July 2022 (cut-off for primary analysis) Completion date: 12 September 2023 (last patient last visit)	**Phase of development of the study:** Phase III	
Objectives: **Primary**: To demonstrate the superiority of trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab (Bev) over FTD/TPI monotherapy in terms of Overall Survival (OS) in patients with refractory metastatic colorectal cancer (mCRC). **Secondary**: To estimate the effect of FTD/TPI in combination with Bev vs FTD/TPI monotherapy in terms of: - Progression-free survival. - Overall response rate. - Disease control rate in patients with refractory mCRC. - To compare the safety and tolerability. - Impact on quality of life.		

Methodology:
This was a multinational, open-label, controlled two-arm, randomised phase III comparison study evaluating the efficacy and safety of FTD/TPI in combination with Bev versus FTD/TPI monotherapy in patients with refractory mCRC.
Patients were randomly assigned in a (1:1) ratio to receive FTD/TPI plus Bev (experimental arm) or FTD/TPI as monotherapy (control arm). The stratification factors were Geographic region (North America, European Union, Rest of the World); time since first metastasis diagnosis (< 18 months, ≥ 18 months); RAS status (wild type, mutant).

The main CSR of 02 December 2022 presented the results of the primary OS analysis once the 331st OS event had been observed (data survival cut-off date of 19 July 2022) as well as other clinical data (cut-off date of 05 July 2022). The present final CSR describes the results based on all data collected from study start up to study completion. Exposure and safety are being updated, but no additional efficacy results are being reported.

This study was performed in strict accordance with Good Clinical Practice (GCP).

Number of patients:
Planned: 490 patients (245 patients per each group).
Randomised: 492 patients in total, 246 patients in each group.

Diagnosis and main criteria for inclusion:

- Male or female participant 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 tumour biopsy.
- Had received a maximum of 2 prior chemotherapy regimens for the treatment of advanced colorectal cancer (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, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody and/or an anti-epidermal growth factor receptor monoclonal antibody 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 Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.
- Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1.
- Adequate organ function based on laboratory values.

Of note: prior anti-VEGF monoclonal antibody was optional except in France, where it was mandated.

Test drug: FTD/TPI + Bevacizumab
FTD/TPI (35 mg/m²/dose) was administered orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenous) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.

Comparator: FTD/TPI
FTD/TPI (35 mg/m²/dose) was administered orally BID, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest. This treatment cycle was repeated every 4 weeks.

Duration of treatment:
Active Treatment period: Patients were treated until they met a discontinuation criterion. Patients were on treatment as long as they continued FTD/TPI. Bevacizumab monotherapy was not allowed.

Follow-up period:
After the withdrawal visit, all treated patients were followed every 8 weeks:

- For tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy.
- For survival status until death or until end of the study was reached (whichever occurred first).

Criteria for evaluation:
Efficacy measurements:
Tumour evaluations were performed based on investigator assessment as per RECIST 1.1 at baseline and then every 2 cycles from Cycle 1 Day 1 (C1D1) until radiologic progression or end of study.
Safety measurements:
Standard safety monitoring was performed including physical examination, vital signs, ECOG PS, 12-lead ECG, adverse events and clinical laboratory evaluations. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Other measurements:
Quality of life assessments were performed at baseline, at each cycle and at withdrawal visit using EORTC QLQ-C30 and EQ-5D-5L questionnaires.

Statistical methods:
Analysis Set:

- Full Analysis Set: based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System. Patients were analysed in the arm they were assigned by randomisation.
- Safety Set (SS): all patients having taken at least one dose of FTD/TPI.

Efficacy and Quality of Life: no update was performed at the end of the study.
Safety analysis: descriptive statistics were provided based on the SS.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS
At the data cut-off date for primary OS analysis, out of the 492 treated patients, 36 were still on treatment. At the study completion date, patients ongoing in the follow-up period had undergone their last contact interaction and those still on treatment were switched to marketed drug in their countries.

BASELINE CHARACTERISTICS
See the main Clinical Study Report (CSR) (NP42261).

UPDATED EXTENT OF EXPOSURE
The mean ± standard deviation (SD) (median) treatment duration was longer in the FTD/TPI + Bev group than in the FTD/TPI group: 6.9 ± 5.9 (5.1) months *vs* 3.5 ± 3.0 (2.1) months. The mean ± SD (median) relative dose intensity (RDI) for FTD/TPI was similar in the FTD/TPI + Bev group and in the FTD/TPI group: 84.7 ± 13.4 (88.0%) *vs* 87.3 ± 14.1 (90.4%), respectively. Regarding administration postponed *i.e.* cycle initiation delayed, and unplanned intra-cycle treatment interruption, results were very similar to those in the main CSR. The percentage of patients who had at least one FTD/TPI dose reduction was similar in the two groups: 17.9% *vs* 12.6%. In the FTD/TPI + Bev group, the mean ± SD (median) RDI for bevacizumab was 86.8 ± 27.3 (87.7%). The mean ± SD (median) number of bevacizumab infusions was 12.5 ± 10.8 (9.0) with full dose of bevacizumab administered at each infusion. The percentage of patients with at least one bevacizumab missed intake was 40.7% (median number of cycles with missed intake was 1.0).

EFFICACY RESULTS
See the main Clinical Study Report (CSR) (NP42261).

SAFETY RESULTS

- **Emergent adverse events (EAEs)**

The main results of adverse events in the Safety Set are summarised in Table 3.

Table 3 - Overall summary for emergent adverse events in the Safety Set (N = 492)

		FTD/TPI + Bev (N = 246)	FTD/TPI (N = 246)
Patients having reported at least one:			
EAE	n (%)	241 (98.0)	241 (98.0)
Treatment-related[1] EAE	n (%)	223 (90.7)	203 (82.5)
Severe (Grade ≥ 3) EAE	n (%)	181 (73.6)	171 (69.5)
Severe treatment-related[1] EAE	n (%)	150 (61.0)	113 (45.9)
Serious EAE (SEAE)	n (%)	66 (26.8)	79 (32.1)
Serious treatment-related[1] EAE	n (%)	15 (6.1)	22 (8.9)
EAE leading to FTD/TPI withdrawal	n (%)	32 (13.0)	31 (12.6)
Treatment-related EAE leading to FTD/TPI withdrawal[2]	n (%)	7 (2.8)	6 (2.4)
Severe EAE leading to FTD/TPI withdrawal[2]	n (%)	22 (8.9)	20 (8.1)
Serious EAE leading to FTD/TPI withdrawal[2]	n (%)	20 (8.1)	17 (6.9)
EAE leading to FTD/TPI treatment delayed	n (%)	168 (68.3)	148 (60.2)
EAE leading to FTD/TPI dose reduction	n (%)	21 (8.5)	21 (8.5)
EAE leading to FTD/TPI treatment delayed and dose reduction	n (%)	31 (12.6)	11 (4.5)
EAE leading to FTD/TPI temporary interruption	n (%)	28 (11.4)	21 (8.5)
EAE leading to bevacizumab withdrawal	n (%)	38 (15.4)	NA
EAE leading to bevacizumab treatment delayed	n (%)	173 (70.3)	NA
EAE leading to bevacizumab temporary interruption	n (%)	66 (26.8)	NA
Patients who died during the study			
During treatment period	n (%)	13 (5.3)	25 (10.2)
During the follow-up period	n (%)	195 (79.3)	199 (80.9)
Treatment-related[1] EAE leading to death	n (%)	-	-

NA not applicable
1. In the FTD/TPI + Bev group, EAEs related to the combination i.e. related to FTD/TPI and/or bevacizumab
2. FTD/TPI withdrawal corresponded to treatment withdrawal as bevacizumab monotherapy was not allowed.

The ***most frequently reported System Organ Classes*** (SOCs) (≥ 50% in either group) were Blood and lymphatic system disorders (74.0% in the FTD/TPI + Bev group and 69.9% in the FTD/TPI group), Gastrointestinal disorders (65.0% and 55.7%, respectively) and General disorders and administration site conditions (50.8% and 48.8%, respectively) with similar frequency in the two groups (between-group difference ≤ 10%). Among other SOCs, the frequencies were similar in the two treatment groups, except for Investigations, which occurred at > 10% higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 41.1% vs 29.7%.

The ***most frequent EAEs*** (> 20% in either group) were neutropenia (62.2% in the FTD/TPI + Bev group *vs* 51.2% in the FTD/TPI group), nausea (38.6% *vs* 28.0%), anaemia (32.1% *vs* 32.5%), asthenia (24.8% *vs* 23.6%), decreased appetite (22.4% *vs* 15.9%), diarrhoea (22.0% *vs* 19.1%), fatigue (22.0% *vs* 16.7%), and vomiting (20.7% *vs* 14.6%). Among those EAEs, neutropenia, nausea, decreased appetite, fatigue and vomiting occurred at higher frequency in the FTD/TPI + Bev group (between-group difference > 5%). Other EAEs occurring at higher frequency in the FTD/TPI + Bev group were thrombocytopenia (17.9% *vs* 11.8%), neutrophil count decreased (13.8% *vs* 7.3%), stomatitis (11.8% *vs* 4.1%), hypertension (10.6% *vs* 2.0%) and platelet count decreased (9.8% *vs* 2.4%).

The percentages of patients who experienced ***severe (Grade ≥ 3) EAEs*** was similar in the FTD/TPI + Bev group and in the FTD/TPI group: 73.6% vs 69.5%. The most frequent (> 10 % in either group) severe EAEs were neutropenia, which occurred at higher frequency in the FTD/TPI + Bev group (43.9% *vs* 32.1% in the FTD/TPI group) and anaemia, which occurred at lower frequency in the FTD/TPI + Bev group (6.9% *vs* 11.0% in the FTD/TPI group).

The percentage of patients who experienced at least one ***treatment-related EAE*** was higher in the FTD/TPI + Bev group than in the FTD/TPI group: 90.7% vs 82.5%. The most frequent (> 20 % in either group) treatment-related EAEs were neutropenia, nausea and anaemia. Among those EAEs, neutropenia and nausea occurred at higher (between-group difference > 5%) frequency in the FTD/TPI + Bev group than in the FTD/TPI group (neutropenia: 60.6% *vs* 48.4%; nausea: 34.1% *vs* 21.1%) and anaemia occurred with similar frequency in the two treatment groups (26.4% *vs* 26.0%). Other treatment-related EAEs occurring at higher frequency in the FTD/TPI + Bev group were thrombocytopenia (16.3% *vs* 9.3%), vomiting (18.7% *vs* 11.0%), neutrophil count decreased (13.8% *vs* 7.3%), decreased appetite (13.4% *vs* 7.7%), stomatitis (11.4% *vs* 4.1%), platelet count decreased (9.8% *vs* 2.0%) and hypertension (7.7% *vs* none). Severe treatment-related EAEs were reported with higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 61.0% *vs* 45.9%. The most frequent (> 5% in either group) ***severe treatment-related EAEs*** reported with > 2% between-group differences were neutropenia and neutrophil count decreased with higher frequency in the FTD/TPI + Bev group (42.3% *vs* 29.3% and 8.9% *vs* 5.3%, respectively), and anaemia with lower frequency in the FTD/TPI + Bev group (5.7% *vs* 8.1%). Among other severe treatment-related EAEs, hypertension was reported with > 2% between-group difference: 4.5% in the FTD/TPI + Bev group while not reported in the FTD/TPI group.

EAEs leading to treatment withdrawal were reported for 13.0% of patients in the FTD/TPI + Bev group *vs* 12.6% in the FTD/TPI group. These EAEs that occurred in more than 1 (0.4%) patient were asthenia (3.3% in the FTD/TPI + Bev group *vs* 0.4% in the FTD/TPI group), decreased appetite (0.8% *vs* 0.4%), biliary dilatation, blood bilirubin increased and pain (0.8% *vs* none, each), anaemia (0.4% *vs* 1.2%), fatigue, intestinal obstruction, jaundice and malignant neoplasm progression (0.4% *vs* 0.8%, each), metastases to central nervous system (none *vs* 0.8%, each). Treatment-related EAEs leading to treatment withdrawal were reported for 2.8% of patients in the FTD/TPI + Bev group *vs* 2.4% in the FTD/TPI group. These EAEs that occurred in more than 1 (0.4%) patient were anaemia (0.4% *vs* 1.2%) and fatigue (none *vs* 0.8%).
In the FTD/TPI + Bev group, 15.4% of patients experienced at least one ***EAE leading to bevacizumab withdrawal***. These EAEs that occurred in more than 1 patient were asthenia (3.3%), pain, biliary dilatation, blood bilirubin increased, decreased appetite, proteinuria and pulmonary embolism (0.8% each).

EAEs leading to FTD/TPI treatment cycle delayed were reported at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 68.3% *vs* 60.2%. The most common of these EAEs were neutropenia (48.4% *vs* 41.5%) and neutrophil count decreased (11.8% *vs* 6.1%). ***EAEs leading to FTD/TPI dose reduction*** were reported with the same frequency in both treatment groups (8.5%). The most common of these EAEs was neutropenia (4.1% *vs* 2.8%) and diarrhoea (0.4% *vs* 2.0%). ***EAEs leading to delayed FTD/TPI treatment and dose reduction*** were reported at higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 12.6% *vs* 4.5%. The most common of these EAEs was neutropenia (9.3% *vs* 2.4%).
In the FTD/TPI + Bev group, 70.3% of patients experienced at least one ***EAE leading to bevacizumab treatment delayed***. The most common of these EAEs were neutropenia (50.0%) neutrophil count decreased (11.8%), COVID-19 (4.9%), thrombocytopenia (3.3%), anaemia (2.8%), asthenia (2.4%).

The percentage of patients who experienced ***serious EAEs*** (SEAEs) was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 26.8% *vs* 32.1%. The most frequent SEAEs (≥ 2%) were intestinal obstruction (3.7% in the FTD/TPI + Bev group *vs* 2.0% in the FTD/TPI group), malignant neoplasm progression (2.4% *vs* 4.5%), COVID-19 (2.0% *vs* 2.4%), anaemia (1.2% *vs* 3.7%), febrile neutropenia (0.4% *vs* 2.4%), jaundice and hepatic failure (0.4 *vs* 2.0% each). Treatment-related SEAEs were reported for 6.1% *vs* 8.9%, respectively; those occurring in more than 2 (0.8%) patients were anaemia (1.2% vs 2.8%) and febrile neutropenia (0.4% vs 2.4%).

A total of 432 patients have ***died***: 84.6% of patients in the FTD/TPI + Bev group and 91.1% of patients in the FTD/TPI group. Among those, 38 patients died during the treatment period (5.3% and 10.2% of patients, respectively) and 394 patients died during the follow-up period (79.3% and 80.9% of patients, respectively). The percentage of patients who experienced at least one EAE leading to death was lower in the FTD/TPI + Bev group than in the FTD/TPI group: 5.7% *vs* 11.0. Fatal EAEs reported in more than one patient were malignant neoplasm progression (6 patients, 2.4% *vs* 11 patients, 4.5%), hepatic failure (1 patient, 0.4% *vs* 3 patients, 1.2%), septic shock (2 patients, 0.8% *vs* none), multiple organ dysfunction syndrome and cachexia (none vs 2 patients, 0.8% for each of these EAEs). For most of patients who experienced fatal EAEs, death was related to disease progression: 3.7% in the FTD/TPI + Bev group vs 8.9% in the FTD/TPI group. None of the fatal EAEs were considered treatment-related in either group.
Out of the 394 patients who died during follow-up period, most of the deaths were attributed to progressive disease: 96.4% in the FTD/TPI + Bev group and 93.9% in the FTD/TPI group.

- **Laboratory tests**

For the biochemistry parameters, treatment-emergent severe abnormalities in ≥ 5% of patients were observed for high bilirubin with similar frequency in the two groups: 6.2% in the FTD/TPI + Bev group *vs* 5.8% in the FTD/TPI group.

For the haematological parameters, treatment-emergent severe low neutrophils values were observed with higher frequency in the FTD/TPI + Bev group than in the FTD/TPI group: 52.5% *vs* 38.6%. For other haematological parameters, between-group differences were ≤ 10%.

CONCLUSION

In this phase III comparative study, 492 patients were randomised to evaluate the efficacy and safety of FTD/TPI in combination with bevacizumab vs FTD/TPI monotherapy in patients with refractory mCRC who have received a maximum of 2 prior chemotherapy regimens for advanced CRC and had demonstrated progressive disease or intolerance to their last regimen.

Similar to results presented in the main CSR, the safety profile of the combination FTD/TPI with bevacizumab was generally consistent with that of each drug toxicity profile except for an increased incidence of neutropenia events compared to FTD/TPI monotherapy.

The results of this final analysis of the SUNLIGHT study confirm the previously reported safety conclusion in the main CSR for the combination of FTD/TPI and bevacizumab with no new clinically relevant safety findings observed.

Date of the report: 09 February 2024

Version of the report: Final version