2. SYNOPSIS

Name of Sponsor: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France** **Les Laboratoires Servier, 50 rue Carnot - 92284 Suresnes Cedex – France**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S95005 (TAS-102) Trifluridine (FTD) and tipiracil hydrochloride (TPI)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: open-label multicentre confirmatory study of efficacy and safety of S95005 (TAS-102) in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies Protocol No.: CL2-95005-003 EudraCT No.: not applicable The description of the study protocol given hereafter includes the modifications of 1 substantial amendment to the protocol.		
Coordinator [redacted]		
Study centres: 2 centres located in Russia included 26 patients		
Publication (reference): Mayer RJ *et al*. RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19.		
Studied period: Initiation date: 03 March 2017 (first visit of first patient) Cut-off date: 31 December 2017 Completion date: 03 December 2018 (last follow-up visit of last patient)	**Phase of development of the study:** Phase II	
Objectives: **Primary objective** The primary objective was to evaluate the efficacy of S95005 in patients with metastatic colorectal cancer (mCRC) who were refractory or intolerant to standard chemotherapies in terms of Progression-Free Survival (PFS) rate at 2 months. **Secondary objectives** - Progression-Free Survival (PFS). - Overall Response Rate (ORR). - Disease Control Rate (DCR). - Safety and tolerability profile of S95005.		
Methodology: This was a single country (Russia), multicentre, open-label, single-arm study of S95005, in patients with mCRC who were refractory or intolerant to standard chemotherapies. This study was performed in strict accordance with Good Clinical Practice.		
Number of patients: Planned: 26 patients. Included: 26 patients.		

Diagnosis and main criteria for inclusion:
Male or female patients aged ≥ 18 years, with histologically or cytologically confirmed adenocarcinoma of the colon or rectum, who had been previously treated by at least 2 prior regimens of standard chemotherapies for mCRC [including fluoropyrimidines, irinotecan, oxaliplatin, and if accessible an anti-Vascular Endothelial Growth Factor (VEGF) monoclonal antibody, and at least one of the anti-Epidermal Growth Factor Receptor (EGFR) monoclonal antibodies for RAS wild-type patients (if RAS mutation status was evaluated)], and was refractory or intolerant to those chemotherapies, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1, and at least one measurable metastatic lesion(s), as defined by Response Evaluation Criteria in Solid Tumor (RECIST), version 1.1 (2009) assessed by Computed Tomography scan performed within 28 days prior to inclusion, and with adequate organ function regarding defined laboratory values.

Test drug:
S95005 containing trifluridine and tipiracil hydrochloride as active ingredients was administered at 35 mg/m²/dose orally twice a day, within 1 hour after completion of morning and evening meals, for 5 days on/2 days off, over 2 weeks, followed by a 14-day rest period. This treatment cycle was repeated every 4 weeks until treatment withdrawal criteria were met.

Comparator: Not applicable.

Screening period: up to 28 days prior to first Investigational Medicinal Product (IMP) intake.
Treatment period: patients received S95005 until a discontinuation criterion was met. The maximum number of cycles was at the discretion of the investigator.
End of study period: withdrawal visit up to 4 weeks after the last S95005 intake.
Tumour assessment follow-up period: only for patient discontinuing treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects).

Criteria for evaluation:
Efficacy measurements:
Tumour assessments using RECIST 1.1 were assessed every 8 weeks:

- Until radiological progression or death (whichever occurred first) during the treatment period.
- Until radiological progression or death, or the start of new anticancer treatment, during the follow-up period.

Safety measurements:
Adverse events (AEs) graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, clinical laboratory evaluation, physical examination and vital signs, ECOG performance status (ECOG-PS), and 12-lead electrocardiogram (ECG).

Statistical methods:

Analysis Set:
Full Analysis Set (FAS): based on the intention-to-treat principle and ICH E9 guideline, all registered patients who had taken at least one dose of IMP and who had no relevant deviation at baseline.
Additionally, a Tumour Response (TR) population was defined which was identical to FAS.

Efficacy analysis:
Primary endpoint:
The primary efficacy endpoint was the progression-free survival rate (PFS Rate) at 2 months corresponding to the first Tumour Assessment (TA) planned 8 weeks after first IMP intake. PFS was defined as the time from the date of registration until the date of the investigator-assessed radiological disease progression or death due to any cause. In the primary analysis, the PFS Rate at 2 months was provided in the FAS with its corresponding 2-sided 95% Clopper-Pearson Confidence Interval (CI).

$$\text{PFS Rate at 2 months} = \frac{\text{"non PD"}}{\text{"PD or death"} + \text{"NE for PFS Rate"} + \text{"}non\ PD\text{"}}$$

non PD patients alive with evidence of non-PD at the first planned TA (8 weeks +/- 7 days). Of note, any TA beyond 8 weeks showing Complete Response (CR), Partial Response (PR) or Stable Disease (SD) as overall response provided evidence of non-progression at 2 months; PD or death Patients who died or progressed within 2 months; NE for PFS Rate patients alive without PD at 2 months but with no evidence of non-progression at 2 months. NE non evaluable.

Assuming an alternative hypothesis of 50% PFS Rate at 2 months and null hypothesis of 20% PFS Rate at 2 months, 26 included patients were required to maintain a 5% type I error and 10% type II error. The study was considered successful if at least 10 non-PD patients were achieved at 2 months.

Statistical methods:

Efficacy analysis:

Secondary endpoint:
The PFS was summarised using Kaplan Meier curves and further characterised in terms of the median and survival probabilities at 2, 4, 6, and 8 months along with the corresponding 2-sided 95% CI for the estimates.
DCR [defined as the proportion of patients with objective evidence of confirmed CR or PR, or SD and ORR (defined as the proportion of patients with objective evidence of confirmed CR or PR)] were described both in the FAS and TR populations with their 2-sided 95% Clopper-Pearson CIs.

Study outcome and safety analysis: descriptive statistics were provided.

The primary analysis, performed when the primary endpoint was reached (PFS at 2 months, cut-off of 31 December 2017), has been described in the primary clinical study report (CSR). The final analysis performed at the end of the study (defined as the date of last follow-up of the last patient) included same analyses as those done for the primary analysis, and is the object of the present final CSR.

SUMMARY – CONCLUSIONS

The primary CSR was issued on 05 October 2018 based on data cut-off date on 31 December 2017. At this time, 4 patients were still on treatment. The present final CSR is based on updated data on 15 February 2019 (final database lock).

DISPOSITION OF PATIENTS
Among the 26 patients included, most of them (23 patients, 88.5%) were withdrawn for progressive disease (including the 4 patients who were still on treatment at the cut-off date). Other reasons were adverse event, non-medical reason and physician decision (1 patient, 3.9%, for each).

BASELINE CHARACTERISTICS
Patients were Caucasian, on average 58.9 ± 11.0 years old, and most of them were 65 years old or younger (18 patients, 69.2%). Most of the patients were female (19 patients, 73.1%). At inclusion in the study, patients had a mCRC for 3.3 ± 2.0 years in average, and the time since diagnosis of the first metastasis was 26.2 months (median). The primary diagnosis of m CRC was adenocarcinoma mostly of colon (61.5%), then rectal (30.8%) and colorectal (7.7%). For the colon, localisation was mainly on left colon (42.3%), then on the right colon (15.4%) and on the transverse colon (3.9%). Patients had mostly at least 3 metastatic sites (24 patients, 92.3%). All but one patient (considered as having a protocol deviation at inclusion, and therefore excluded from the FAS and TR) had received at least 2 lines of prior systemic therapy for mCRC, and most of patients had received 4 lines and more (18 patients, 69.2%). All patients (n = 26) were previously treated with irinotecan, oxaliplatin and fluoropyrimidine treatment [(including fluorouracil, 24 patients (92.3%) and capecitabine, 19 patients (73.1%)]. In addition, 19 patients, 73.1%, received bevacizumab in combination with above chemotherapies. At entry in the study, all patients had at least one measurable target lesion. All but one patient underwent surgery, and about one third of patients (34.6%) had received radiotherapy. Most of patients (61.5%) had received both surgery and chemotherapy.
Among patients for whom a biopsy was performed (n = 25), about half were KRAS wild type (13 patients, 52.0%), and patients who were assessed for the BRAF status (n = 17) were all wild type. Regarding ECOG PS, patients were mainly rated 1 (22 patients, 84.6%), and 4 patients (15.4%) had an ECOG PS rated 0.

EXTENT OF EXPOSURE
Updated extent of exposure was as follows. Treatment duration was on average 25.1 ± 22.2 weeks (median = 16.6 weeks) in the Safety Set (N = 26). The number of cycles underwent by patients was in average 5.8 ± 5.2, and about one third of patients (30.8%) underwent more than 6 cycles. One patient reached a maximum of 21 cycles of treatment. Half of the patients had at least one cycle delayed, mainly due to medical reasons (90.9%, all AEs), and 8 patients, 30.8% had at least one cycle with dose reduced. Emergent adverse events (EAEs) leading to cycle delay or dose reduced are presented in the safety results section. The Relative Dose Intensity [(RDI, defined as the ratio of the dose intensity (mg/m²/week) to the initial planned dose intensity depending on the schedule)] was on average 88.3 ± 10.6%, and most of patients (80.8%) had RDI comprised in the]80-100%] class.

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

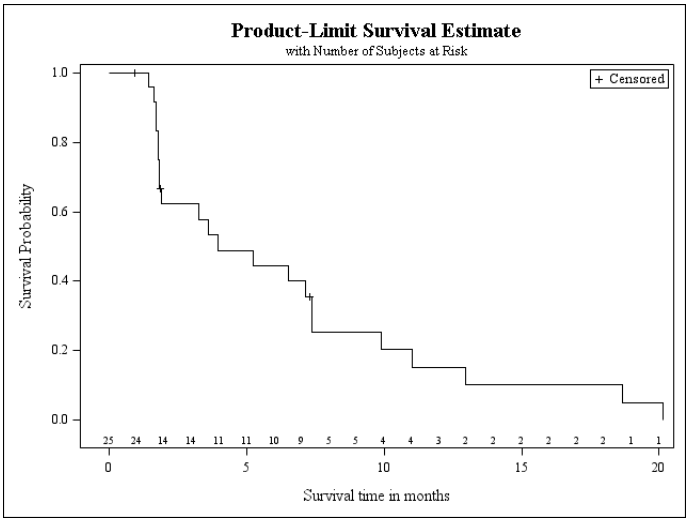
- **Primary efficacy endpoint**

As expected, at final data lock , the PFS Rate evaluated at 2 months showed the same results as the ones observed from the primary analysis: 52.0% (13/25 patients) with 95% CI [31.3 ; 72.2] in the FAS. As non PD was obtained for 13 patients, the study was considered successful.

- **Secondary efficacy endpoints**
  - **Progression Free Survival**

Results for PFS were similar to the primary analysis: the median of the PFS was 4.0 months with a 95% CI = [1.8 ; 7.4]. The survival probability was 0.6 at 2 months (95% CI = [0.4 ; 0.8]), and then decreased to 0.5 at 4 months (95% CI = [0.3 ; 0.7]), to 0.4 at 6 months (95% CI = [0.2 ; 0.6]). At final analysis, in addition since the cut-off date, the survival probability at 8 months was evaluated at 0.3 (95% CI = [0.1 ; 0.45]).

Kaplan-Meier curves of the PFS in the FAS (N = 25)



- **Objective Response Rate (ORR) and Disease Control Rate (DCR)**

  Updated results at final data lock are unchanged for ORR and DCR. A majority of the patients (15 patients, 60.0%) had a stable disease, 9 patients (36.0%) had a progressive disease, and one patient was non-evaluable. The corresponding ORR was 0 (95% CI = [0 ; 13.7]) and the DCR was 60.0% with a corresponding 95% CI = [38.7 ; 78.9]. The updated mean duration of the disease control was 8.4 ± 5.5 months (median = 7.3 months), and for most of patients (73.3%), it was ≥ 4 months (complementary analysis).

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

At final data lock, there was no relevant change in the safety profile compared to the initial cut-off data.
Main results for EAE in the Safety Set are presented in the Table hereafter.

Overall summary for adverse events in the Safety Set

		S95005 (N = 26)
Patients having reported at least one:		
Emergent Adverse Event (EAE)	n (%)	26 (100)
Treatment-related EAE	n (%)	20 (76.9)
Severe EAE (grade ≥ 3)	n (%)	23 (88.5)
Treatment-related	n (%)	17 (65.4)
Serious EAE (including death)	n (%)	11 (42.3)
Treatment-related	n (%)	5 (19.2)
EAE leading to treatment withdrawal	n (%)	2 (7.7)
Due to severe EAE	n (%)	1 (3.8)
Due to serious EAE	n (%)	-
Due to Treatment-related EAE	n (%)	1 (3.8)
Due to severe Treatment-related EAE	n (%)	1 (3.8)
Due to Treatment-related serious EAE	n (%)	-
Patients who died	n (%)	3* (11.5)

** During the follow-up period*

All patients experienced at least one EAE. Most frequently reported preferred terms (PTs) were neutropenia (18 patients, 69.2%), malignant neoplasm progression (15 patients, 57.7%) the following PTs that occurred in 8 patients (30.8%) each one: anaemia, asthenia, decreased appetite, and diarrhoea, and in 7 patients, 26.9% each one: fatigue, and nausea. More than half of the EAEs (56.6%) were resolved. Overall, 88.5% of the patients (23 patients) were affected by severe EAEs (*i.e.* rated grade ≥ 3 according to CTCAE). Severe EAEs were mainly neutropenia (12 patients, 46.2%), malignant neoplasm progression (7 patients, 26.9%), and anaemia (5 patients, 19.2%). Of note, all febrile neutropenia that occurred in 3 patients (11.5%), were rated grade 3, and resolved within 10 days or less.
Treatment-related EAEs occurred in most of the patients (20 patients, 76.9%), and included mainly neutropenia (18 patients, 69.2%), diarrhoea (8 patients, 30.8%), nausea, decreased appetite: 7 patients, 26.9% each one, and fatigue, anaemia: 6 patients, 23.1%, each one. Most of severe EAEs were considered as treatment-related by the investigator (17 patients, 65.4%) mainly due to neutropenia (12 patients, 46.2 %). Among other severe treatment-related EAEs, those reported in at least 2 patients were anaemia (4 patients, 15.4%), febrile neutropenia (3 patients, 11.5%) and GGT increased (2 patients, 7.7%).
Half of the patients had at least one EAE leading to dose delayed (without concomitant dose reduction) including neutropenia for all these patients. EAE led to dose reduction (fatigue) in one patient (3.8%). In addition, EAEs led both to dose delayed and dose reduction in 5 patients (19.2% of patients), including neutropenia and febrile neutropenia (one patient each one).
EAE led to IMP withdrawal in 2 patients (7.7%) due to general physical health deterioration (grade 3, considered as treatment-related) and malignant neoplasm progression (grade 1), none of these EAEs was serious.
Serious EAEs were reported in 11 patients (42.3%), including mostly malignant neoplasm progression (4 patients, 15.4%), febrile neutropenia (3 patients, 11.5%), and anaemia (2 patients, 7.7%). Most of these patients (9/10) had at least one serious EAE rated grade ≥ 3. Serious EAEs considered as treatment-related affected 5 patients (19.2%), including febrile neutropenia (3 patients, 11.5%), and anaemia (2 patients, 7.7%). Since the cut-off, one additional patient experienced a SEAE intestinal obstruction (not considered as treatment-related).
No death occurred during the treatment period and no additional death was reported since the cut-off date during the study. A total of 3 patients (11.5%) had EAEs leading to death during the follow-up period, due to malignant neoplasm progression, not considered as treatment-related by the investigator.

- **Blood laboratory tests**

The updated results related to laboratory parameters did not show relevant difference from the ones observed at initial cut-off.

- **Vital signs and ECOG PS**

The updated results related to vital signs and ECOG PS did not show relevant difference from the ones observed at initial cut-off, except the body weight with a mean change from baseline of -4.5 ± 5.1 kg.

CONCLUSION

In this open label study conducted in Russia, 26 advanced metastatic colorectal cancer patients were included, and received S95005 administered orally, at 35 mg/m²/dose twice a day, 5 days on/2 days off over 2 weeks, followed by a 14-day rest. In the analysis with the final updated data (including 4 patients who were still on treatment at the cut-off date of the primary analysis), the progression free survival rate evaluated at 2 months (primary efficacy endpoint) was unchanged as expected: 52.0% (13 patients). The study had been confirmed as successful as at least 10 patients with non-progressive disease were observed at 2 months. Best overall response results were unchanged: stable disease (60% of patients), progressive disease (36%) and one non-evaluable patient. In addition, no relevant change was seen in the updated safety results which were in accordance with the known safety profile of S95005. More than half of the patients had their ECOG performance status maintained. These results are in accordance with the safety and efficacy results observed in the S95005 arm within the RECOURSE study which indicate that the Russian patients do not differ from the RECOURSE population.

Date of the report: 13 June 2019

Version of the report: Final version