2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Lonsurf® or 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 (S95005) in combination with bevacizumab to capecitabine in combination with bevacizumab in first-line treatment of patients with metastatic colorectal cancer who are not candidate for intensive therapy (SOLSTICE study).
Protocol No.:CL3-95005-006
EudraCT No.: 2017-004059-22
Universal Trial Number: U1111-1206-3198
ClinicalTrials.gov: NCT03869892
The description of the study protocol given hereafter includes the modifications of the three substantial amendments to the protocol.

International Coordinator
[redacted]

Study countries:
A total of 856 patients were randomised in 25 countries: Ukraine (132), Russian Federation (126), Spain (83), Hungary (74), Italy (57), United Kingdom (53), Brazil (42), Denmark (36), Poland (34), France (33), Bulgaria (23), Romania (23), Netherlands (21), Argentina (15), Australia (15), Estonia (14), Lithuania (14), Austria (13), Czech Republic (12), Latvia (11), Sweden (10), Portugal (6), Slovakia (4), Germany (3), Ireland (2).

Publication (reference):
Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 21 March 2019 (first visit first patient) Data cut-off date: 09 June 2021 (occurrence of 628th PFS event)	Phase III

Objectives:

Primary
To demonstrate the superiority of S95005 in combination with bevacizumab over capecitabine in combination with bevacizumab in terms of Progression-free survival (PFS) based on Investigator assessment.

Secondary
Overall survival (OS), overall response rate (ORR), disease control rate (DCR), duration of response (DoR), time to treatment failure (TTF), safety and tolerability, quality of life (QoL).

Exploratory
Compare the efficacy of S95005 in combination with bevacizumab to capecitabine in combination with bevacizumab according to RAS, BRAF and MSI status.

Methodology:
This was an international, open-label, controlled two-arm, randomised phase III study comparing S95005 in combination with bevacizumab *versus* (*vs*) capecitabine in combination with bevacizumab in the first-line treatment of patients with unresectable metastatic colorectal cancer (mCRC) who were not candidate for intensive therapy.
Patients were randomised in a (1:1) ratio. The stratification factors were Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 *vs* 1 *vs* 2), primary tumour localisation (right *vs* left) and reason why the patient was not candidate to intensive therapy (clinical condition reason *vs* non-clinical condition reason).

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

Number of patients:
Planned: 854 patients in total (427 patients per each group).
Randomised: 856 patients in total, 426 patients in the S95005 + bevacizumab group (S95005 + Bev) and 430 in the capecitabine + bevacizumab group (Cap + Bev).
Number of PFS events for the final primary analysis: 628 events.
Number of PFS events for the interim primary analysis: 80% of the total number of events *i.e.*502 events.

Diagnosis and main criteria for inclusion:
Male or female participant aged ≥ 18 years old, having definitive histologically confirmed adenocarcinoma of the colon or rectum, with at least one measurable metastatic lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, RAS status determined on tumour biopsy, not a candidate for standard full dose combination chemotherapy with irinotecan or oxaliplatin, not a candidate for curative resection of metastatic lesions, ECOG PS ≤ 2, and with adequate organ function based on laboratory test results.
Patients should have not received previous systemic anticancer therapy for unresectable metastatic colorectal cancer, including systemic use of chemotherapy agents as radiosensitizers. Previous adjuvant or neoadjuvant chemotherapy was allowed only if the patient has been disease free for at least 6 months after the completion of the chemotherapy.

Test drug: S95005 + Bev
S95005 (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 [IV]) administered every 2 weeks (Day 1 and Day 15). This treatment cycle was repeated every 4 weeks.
Batch numbers:
- S95005 15 mg tablet: [redacted].
- S95005 20 mg tablet: [redacted].
- Bevacizumab 4 mL vial: [redacted]
- Bevacizumab 16 mL vial: [redacted]

Comparator: Cap + Bev
Capecitabine (1250 mg/m²/dose) was administered orally BID on Days 1–14 of each cycle with bevacizumab (7.5 mg/kg, IV) administered on Day 1 of each cycle. This treatment cycle was repeated every 3 weeks.
Note: according to local clinical practice, the starting dose of capecitabine could be reduced to 1000 mg/m²/dose. In this case, the dose could be re-evaluated at each cycle and further increased to 1250 mg/m²/dose if a good tolerance was observed.
Batch numbers:
- Capecitabine 150 mg tablet: [redacted]
- Capecitabine 500 mg tablet: [redacted]
- Bevacizumab 4 mL and 16 mL vials: see above

Duration of treatment:
Active treatment period:
Patients were treated by the assigned combined regimen until they met a discontinuation criterion. Patients were considered on treatment as long as they continued S95005 or capecitabine. Bevacizumab monotherapy was not allowed.

Follow-up period:
If a patient discontinued study treatment for reasons other than radiologic disease progression (*e.g.*, intolerable side effects or clinical progression), he/she was followed up for tumour response until radiologic disease progression regardless of initiation of a new anticancer therapy.
After radiologic disease progression, the patient was followed up for survival and for date of progression after the second line of chemotherapy (if applicable) until the end of the study *i.e.* 24 months after the first study drug intake of the last randomised patient.

Specific COVID-19 situation
In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT-scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) had to be immediately interrupted. The study treatment(s) could be restarted if patient was asymptomatic and a period of at least 15 days after the diagnosis had been respected with or without new testing (in case of new testing, the result had to be negative).

Criteria for evaluation:
Efficacy measurements:
Tumour assessments were performed as per RECIST (version 1.1, 2009) at baseline and then every 8 weeks (from Day 1 Cycle 1) until radiologic progression or end of study.

Safety measurements:
Standard safety monitoring was performed and adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Other measurements: Quality of life assessments at baseline, every 6 weeks and at withdrawal visit using EORTC QLQ-C30 and EQ-5D-5L questionnaires.

Biomarkers measurements:
Blood samples were collected at baseline for BRAF status evaluation when it was not previously assessed.

Statistical methods:
Sample size determination:
A maximum of 628 PFS events were required for the primary analysis to detect a hazard ratio (HR) of 0.77 with 90% power using a log-rank test and a 2-look group sequential design at one-sided cumulative 2.5% level of significance. Based on the data from the CL2-95005-002 (TASCO1) study, the median duration of PFS in the control group was expected to be around 7.5 months. A HR of 0.77 translated into 2.2 months increase of the median PFS in the experimental group (9.7 months) compared to the control group. Based on the assumption that enrolment continued for approximately 18 months, and that about 10% of the subjects would drop out when reaching 36 months since the randomisation, a total of 854 patients randomised in a 1:1 ratio was needed to observe the 628th PFS events approximately 10 months after the last patient randomisation.

Analysis Sets:
- Full Analysis Set (FAS): based on the intention-to-treat principle, all patients to whom a therapeutic unit was randomly assigned using Interactive Web Response System (IWRS). Patients were analysed in the arm they were assigned by randomization.
- Safety Set (SS): all patients having taken at least one dose of Investigational Medicinal Product (IMP). Patients were analysed according to the treatment actually received.
- QLQ-C30 Set: patients from the FAS having completed at least two thirds (*i.e.* at least 20 questions) of the questions of the baseline QLQ-C30 questionnaire, and at least two thirds of the questions of a QLQ-C30 questionnaire during the study period.
- EQ5D Set: patients from the FAS with an evaluable EQ-5D-5L assessment at baseline and at least one evaluable assessment post baseline. EQ-5D-5L assessment was considered non evaluable when responses were missing for one or more of the dimensions.

Efficacy analysis:
Primary endpoint: PFS
PFS was defined as the time elapsed between the randomisation and the date of radiologic tumour progression or death from any cause. For patients who were lost to follow-up without radiologic progression or reached the time point of analysis without a known record of death or radiologic progression, the PFS was censored at the date of last evaluable tumour assessment:

- Primary analysis: in the FAS, the PFS based on investigator assessment was compared with a stratified log-rank test using the stratification factors based on IWRS. The PFS HR and its corresponding 95% confidence interval (CI) were estimated using a stratified Cox proportional hazard (CPH) model on the stratification factors based on IWRS data. PFS for each group was summarised using Kaplan Meier curves and further characterized in terms of the median and survival probabilities at 6, 12, 18, and 24 months along with the corresponding 2-sided 95% CI for the estimates.
- Sensitivity analyses were carried out in the FAS with PFS based on investigator assessment and with PFS based on Blind Independent Central Review (BICR) assessment.

Secondary endpoint: OS
A maximum of 578 deaths was required for the OS analysis to detect a HR of 0.79 with 80.0% power at one-sided cumulative 2.5% level of significance and tested in a hierarchical approach, *i.e.* OS is tested at 45 months if the PFS has been proven to be statistically significant in a previous analysis.

Other secondary endpoints:
ORR, DCR [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)], DoR and TTF were compared between the two treatment groups with investigator and BICR tumour assessment.
Quality of Life: change from baseline in the global health status score was identified as the primary QoL variable of interest. Other sub-scale scores were identified as secondary QoL variables of interest.

Safety analysis: descriptive statistics were provided.

Interim analysis:
As planned per study protocol, an interim PFS analysis was performed by the independent statistician of the DMC when 502 PFS events were observed. The DMC recommendation was to continue the trial as per protocol and analyse the primary endpoint when the total number of PFS events have been reached *i.e.* 628 events. Results of this final PFS analysis and of other clinical data are presented in the present clinical study report (CSR).

SUMMARY - CONCLUSIONS
A total of 1059 patients were selected. Of those, 203 patients (19.2%) were neither included nor randomised due to non-compliance with inclusion/non-inclusion criteria (17.5%), patient consent withdrawal (1.2%), non-fatal adverse event (3 patients, 0.3%) and fatal adverse events (2 patients, 0.2%).

DISPOSITION OF RANDOMISED PATIENTS AND ANALYSIS SETS

Table 1 - Disposition of randomised patients and Analysis Sets

Patient Status		S95005 + Bev (N = 426)	Cap + Bev (N = 430)	All (N = 856)
Randomised	**n**	**426**	**430**	**856**
Randomised - Not included - Not treated*	**n (%)**	**2 (0.47)**	**3 (0.70)**	**5 (0.58)**
Non-compliance with incl./non-inclusion criteria	n (%)	1 (0.23)	2 (0.47)	3 (0.35)
Patient consent withdrawal	n (%)	1 (0.23)	1 (0.23)	2 (0.23)
Randomised - Included - Not treated*	**n (%)**	**1 (0.23)**	**-**	**1 (0.12)**
Other, Medical reason	n (%)	1 (0.24)	-	1 (0.12)
Withdrawn from treatment due to	**n (%)**	**349 (81.92)**	**368 (85.58)**	**717 (83.76)**
Radiological progressive disease	n (%)	168 (39.44)	165 (38.37)	333 (38.90)
Adverse event	n (%)	71 (16.67)	101 (23.49)	172 (20.09)
Clinical progressive disease	n (%)	39 (9.15)	38 (8.84)	77 (9.00)
Radiological and clinical progressive disease	n (%)	34 (7.98)	23 (5.35)	57 (6.66)
Non-medical reason	n (%)	27 (6.34)	26 (6.05)	53 (6.19)
Other, Medical reason	n (%)	8 (1.88)	8 (1.86)	16 (1.87)
Patient becoming resectable	n (%)	2 (0.47)	3 (0.70)	5 (0.58)
Protocol deviation	n (%)	-	3 (0.70)	3 (0.35)
Lost to follow-up	n (%)	-	1 (0.23)	1 (0.12)
Continuing study on-treatment	**n (%)**	**74 (17.37)**	**59 (13.72)**	**133 (15.54)**
Patients not continuing the follow-up period due to	**n (%)**	**163 (38.26)**	**161 (37.44)**	**324 (37.85)**
Death	n (%)	153 (35.92)	154 (35.81)	307 (35.86)
Withdrawal Non-Medical reason	n (%)	9 (2.11)	5 (1.16)	14 (1.64)
Lost to follow-up	n (%)	1 (0.23)	2 (0.47)	3 (0.35)
If death: reason of death	**n**	**153**	**154**	**307**
Progressive disease	n (%)	131 (85.62)	132 (85.71)	263 (85.67)
Other	n (%)	22 (14.38)	22 (14.29)	44 (14.33)

N number of patients by arm; n number of patients; percentages are based on n
incl.= inclusion
** even if non-treated, those randomised patients were in the FAS population with best overall response considered as Non-Evaluable*

Analysis sets		S95005 + Bev	Cap + Bev	All
FAS (randomised patients)	n (%)	426 (49.8)	430 (50.2)	856
QLQ-C30 set	n (%)	366 (50.0)	366 (50.0)	732
EQ5D set	n (%)	364 (50.1)	363 (49.9)	727
BRAFFAS	n (%)	411 (49.3)	422 (50.7)	833
BRAFTUMFAS	n (%)	188 (49.5)	192 (50.5)	380
MSIFAS	n (%)	141 (51.8)	131 (48.2)	272
SS	n (%)	423 (49.8)	427 (50.2)	850

Percentages are based on number of all patients for each analysis set
FAS Full analysis set; BRAFFAS patients of the FAS with BRAF status available; BRAFTUMFAS patients of the FAS with BRAF status available based on tumour biopsy; MSIFAS patients of the FAS with MSI status available; SS Safety Set

BASELINE CHARACTERISTICS

In the FAS, demographic and other baseline characteristics were globally in line with inclusion criteria defined in the study protocol.

The median age was 73.0 years with 76.2% ≥ 65 years, 61.1% ≥ 70 years and 45.7% ≥ 75 years. Overall, 54.4% of patients were male and 96.7% were Caucasian. The treatment groups were well balanced with respect of KRAS, NRAS, BRAF status (wild or mutant) and MSI status (MSI-H or MSS/MSI-L).

At baseline, all patients were diagnosed with CRC metastasis, except for 1 patient randomised not included in S95005 + Bev group with CRC history not documented. The primary tumour site was left colon for 70.1 % of patients and right colon for 29.9%. The mean (median) disease duration from initial CRC diagnosis was 1.4 ± 2.4 years (0.4 years) and mean (median) time from first metastasis to randomisation was 2.0 ± 3.2 months (1.3 month).

The main reason why patient was not candidate for intensive therapy was clinical condition for 67.4% of patients and non-clinical condition for 32.6% of patients. Among those, the most frequently reported reasons were elderly (42.5%), patient preference (18.4%), ECOG PS (15.0%) and low tumour burden (12.8%) with no relevant between-group differences.

Overall, 65.1% of patients received at least one previous therapy for CRC. Previous curative surgery was reported for 46.6% of patients (43.4% in the S95005+ Bev group vs 49.8% in the Cap + Bev group) and previous palliative surgery for 18.3% (22.1% *vs* 14.7%). Previous drug treatments were reported for 25.4% of patients (21.8% *vs* 28.8%) and previous radiotherapy for 12.5% of patients (11.0% *vs* 14.0%).
The majority of patients had an ECOG PS (based on eCRF data) rated 0 or 1 (0: 23.0%, 1: 58.1%, 2: 18.7%). For patients ≥ 70 years, the G8 score was < 14 for 49.8% of patients. The Charlson comorbidity score was 0 for 56.7% of patients, 1-2 for 31.6% and ≥ 3 for 11.7%.

Analyses related to COVD-19 pandemic showed low impact of the pandemic on the study data.

EXTENT OF EXPOSURE

As of cut-off date, the mean (median) treatment duration was longer in the S95005 + Bev group than in the Cap + Bev group: 9.0 ± 5.5 (8.2) months *vs* 7.9 ± 5.2 (7.6) months. In the S95005 + Bev group, the median relative dose intensity (RDI) of S95005 was similar than the RDI of capecitabine in the Cap + Bev group: 85.1% *vs* 85.8%, respectively. The median RDI of bevacizumab was lower in the S95005 + Bev group than in the Cap + Bev group: 84.0% vs 96.4%. For patients who started capecitabine at 1250 mg/m^2, the median RDI of capecitabine was 85.0% and 87.2% for patients who started capecitabine at 1000 mg/m^2.

The majority of patients had at least one cycle delayed with higher frequency in the S95005 + Bev group than in the Cap + Bev group: 75.7% *vs* 54.8%. Few patients had at least one unplanned intra-cycle treatment interruption: 5.2% in each group. The percentage of patients who had at least one cycle with dose reduced was lower in the S95005 + Bev group than in the Cap + Bev group: 35.2% *vs* 47.5%.
In the Cap + Bev group (n = 427), the starting dose of capecitabine was 1000 mg/m^2 for 54.8% of patients and 1250 mg/m^2 for 45.2%. Among patients who received the reduced starting dose of 1000 mg/m^2 (n = 234), the reason of the investigator's choice was age for 58.1% of patients, creatinine clearance for 3.4%, low weight/low BSA for 3.4% and other reason for 35.0%. Among patients who started capecitabine at 1000 mg/m^2, 6.4% were re-evaluated and further treated at 1250 mg/m^2.

EFFICACY RESULTS

Primary efficacy endpoint: PFS based on investigator assessment

- ***Primary PFS analysis in the FAS***:

The study did not demonstrate the statistically significant superiority of S95005 + Bev over Cap + Bev in reducing the risk of disease progression or death. Thus, the primary endpoint was not reached. The estimated HR was 0.87 (95% CI = [0.75; 1.02]) in favour of S95005 + Bev. The median PFS was 9.40 *vs* 9.26 months respectively, with p-value of 0.0464 not reaching the target p-value of 0.021 (stratified log-rank test at one-sided 2.5 level of significance); see Table 2 hereafter.

Table 2: Progression Free Survival - Investigator assessment - FAS (N = 856)

		S95005 + Bev (N = 426)	Cap + Bev (N = 430)
Number of censors	n (%)	117 (27.46)	110 (25.58)
Lost to follow-up without documented radiological PD	n (%)	8 (1.88)	12 (2.79)
Alive without documented radiological PD	n (%)	102 (23.94)	85 (19.77)
No baseline or post-baseline tumour assessment	n (%)	7 (1.64)	13 (3.02)
Number of events*	n (%)	309 (72.54)	320 (74.42)
Radiological progression	n (%)	250 (58.69)	259 (60.23)
Death	n (%)	59 (13.85)	61 (14.19)
Progression Free Survival (months)			
Median (months) (1)		9.40	9.26
95% confidence interval (2)		[9.10 ; 10.94]	[8.90 ; 9.79]
p-value (3)		0.0464	
Progression Free Survival probability			
Survival probability at 6 months (1)		0.71	0.71
95% confidence interval (4)		[0.66 ; 0.75]	[0.66 ; 0.75]
Survival probability at 12 months (1)		0.39	0.31
95% confidence interval (4)		[0.34 ; 0.43]	[0.26 ; 0.36]
Survival probability at 18 months (1)		0.19	0.13
95% confidence interval (4)		[0.15 ; 0.24]	[0.09 ; 0.17]
Survival probability at 24 months (1)		0.09	ND
95% confidence interval (4)		[0.04 ; 0.16]	ND
Hazard ratio (relative to Cap + Bev)**		0.87	
95% confidence interval		[0.75, 1.02]	

Percentages are based on N
(1) Kaplan-Meier estimates
(2) Methodology of Brookmeyer and Crowley
(3) Stratified Log-Rank Test at one-sided 2.5 level of significance (IWRS stratification factors ECOG, tumour localisation, reason the patient was not candidate for intensive therapy)
(4) Using log-log transformation methodology of Kalbfleisch and Prentice
**The primary analysis of PFS included data obtained through the date of the 628th PFS event observed in the study i.e. 09 June 2021. On that day, a 629th event occurred which was taken in account for the PFS analysis.*
*** Stratified Cox proportional hazard model using IWRS stratification factors (see above)*
ND not determined

- ***Sensitivity analyses in the FAS:***

All sensitivity analyses were consistent with the primary PFS analysis, with HRs of 0.86 to 0.91, except the analysis 'clinical progression or new anticancer therapy as PD event in addition to first radiological progression and death' with a trend of effect in favour of S95005 + Bev (HR of 0.84 with 95% CI [0.72, 0.98] not including 1). For the sensitivity analysis using BICR assessment, HR was 0.85 (95% CI = [0.72, 1.00] including 1) and the median PFS was 10.6 months (95% CI = [9.33 ; 11.07]) for the S95005 + Bev group *vs* 9.3 months (95% CI = [9.13 ; 10.15]) for the Cap + Bev group; p = 0.0265, stratified log-rank test.

- ***PFS analysis by subgroup***

For almost all subgroups examined in the FAS, the HR obtained for PFS was consistent with the one in overall population with no statistical difference for S95005 + Bev over Cap + Bev, except for the following particular subgroups with a trend of effect in favour of S95005 + Bev (*i.e.* 95% CI not including 1): male patients, median PFS of 10.3 *vs* 9.2 months, HR = 0.75, 95% CI = [0.61; 0.93]; Neutrophil to Lymphocyte ratio (NLR) < 5: median PFS of 10.8 *vs* 9.3 months, HR = 0.82, 95% CI = [0.69; 0.98], Charlson score 0: median PFS of 11.1 *vs* 9.4 months, HR = 0.75, 95% CI = [0.6 ; 0.93] and RAS wild type: median PFS of 10.7 *vs* 9.3 months, HR = 0.76, 95% CI = [0.6 ; 0.97].

Secondary efficacy endpoints

- ***Overall survival***

According to study protocol, OS analysis will be performed after a maximum of 578 deaths will be collected *i.e.* at approximately 45 months after the start of the study.

Other secondary endpoints based on investigator assessment

- ***Overall response rate, disease control rate***

In the FAS with PFS based on investigator assessment, ORR was 35.9% in the S95005 + Bev group and 41.6% in the Cap + Bev group, mostly PR in both treatment groups, with a non-statistically significant between-group difference of -5.7%. The percentage of patients with SD was 50.5% in the S95005 + Bev group and 43.5% in the Cap + Bev group with a non-statistically significant between-group difference in DCR of 1.27%.

- ***Time to treatment failure***

TTF was the time to treatment discontinuation for any reason. In the FAS, the median TTF was in favour of S95005 + Bev group over Cap + Bev (8.8 *vs* 8.0 months, respectively) with a HR of 0.84 which was statistically significant (95% CI: [0.72, 0.98]; p = 0.0115 stratified log-rank test).

Quality of Life

QLQ-C30 analyses showed no clinically relevant difference (minimally important difference of ± 10 points) in mean change from baseline for the global health in either treatment group, as well as for the functioning and almost all symptom items. Similar results were observed using EQ-5D-5L utility and VAS scores.

SAFETY RESULTS

Emergent adverse events

The main results of EAEs on cut-off date are summarised in the Safety Set in Table 3.

Table 3 - Overall summary for emergent adverse events on cut-off date in the Safety Set (N = 850)

		S95005 + Bev (N = 423)	Cap + Bev (N = 427)
Patients having reported at least one:			
EAE	n (%)	418 (98.8)	412 (96.5)
Treatment-related EAE	n (%)	396 (93.6)	375 (87.8)
Severe (Grade ≥ 3) EAE	n (%)	367 (86.8)	281 (65.8)
Severe treatment-related EAE	n (%)	329 (77.8)	192 (45.0)
Serious EAE (including death) (SEAE)	n (%)	176 (41.6)	197 (46.1)
Serious treatment-related EAE	n (%)	83 (19.6)	96 (22.5)
EAE leading to study drug withdrawal	n (%)	109 (25.8)	132 (30.9)
Treatment-related EAE leading to study drug withdrawal	n (%)	49 (11.6)	68 (15.9)
Severe (Grade ≥ 3) EAE leading to study drug withdrawal	n (%)	74 (17.5)	77 (18.0)
Serious EAE leading to study drug withdrawal	n (%)	55 (13.0)	59 (13.8)
Patients who died during the study*	n (%)	172 (40.7)	177 (41.5)
During treatment period	n (%)	44 (10.4)	43 (10.1)
During the follow-up period	n (%)	128 (30.3)	134 (31.4)

** additionally,5 patients died prior to study treatment: 3 randomised but not included (2 patients in S95005 + Bev group and 1 patient in Cap + Bev group) and 2 patients not randomised.*

Almost all patients experienced at least one EAE: 98.8% in the S95005 + Bev group and 96.5% in the Cap + Bev group. The ***most frequently affected SOCs*** (≥ 50% in either treatment group) were Blood and lymphatic system disorders (80.1% in the S95005 Bev group vs 25.3% in the Cap + Bev group), Gastrointestinal disorders (69.0% *vs* 65.8%), General disorders and administration site conditions (53.4% *vs* 51.1%) and Skin and subcutaneous tissue disorders (17.7% *vs* 59.7%). Among those most common SOCs, the frequencies were similar in the two treatment groups, except for Blood and lymphatic system disorders with higher frequency in the S95005 + Bev group and for Skin and subcutaneous tissue disorders with lower frequency in the S95005 + Bev group (between-group difference > 10%).

Among others SOCs, the frequencies were similar in the two treatment groups, except for Investigations at a higher frequency in the S95005 + Bev group than in the Cap + Bev group: 48.7% *vs* 35.8% (between-group difference > 10%).

The ***most frequent EAEs*** (> 20% in either treatment group) reported were neutropenia (65.7% in the S95005 + Bev group *vs* 8.7% in the Cap + Bev group), palmar-plantar eythrodysaesthesia syndrome (1.2% *vs* 52.7%) anaemia (44.4% *vs* 13.6%), diarrhoea (36.4% vs 34.0%), nausea (35.0% *vs* 23.9%), fatigue (23.9% *vs* 25.1%), decreased appetite (22.5% *vs* 18.0%), asthenia (22.5% *vs* 17.8%) and neutrophil count decreased (21.5% *vs* 2.6%). Among those EAEs, the frequencies were similar in the two treatment groups, except for neutropenia, anaemia, nausea and neutrophil count decreased with higher frequency in the S95005 + Bev group and palmar-plantar eythrodysaesthesia syndrome with lower frequency in the S95005 + Bev group (between-group difference > 5%).

The percentage of patients who experienced ***severe (Grade ≥ 3) EAE*** was higher in the S95005 + Bev group than in the Cap + Bev group: 86.8% *vs* 65.8%. The most frequent (> 10 % in either treatment group) severe EAEs were reported at higher frequency in the S95005 + Bev group for neutropenia (52.0% *vs* 1.4% in the Cap + Bev group), neutrophil count decrease (18.4% *vs* 0.9%) and anaemia (14.2% *vs* 3.7%) and at lower frequency in the S95005 + Bev group for palmar-plantar erythrodysaesthesia syndrome (none *vs* 14.5% in the Cap + Bev group). Severe hypertension was reported in 8.5% *vs* 11.2% of the patients respectively.

The most frequent (> 20 % in either treatment group) ***treatment-related EAEs*** were neutropenia (65.5% in the S95005 + Bev group *vs* 8.4% in the Cap + Bev group), palmar-plantar eythrodysaesthesia syndrome (1.2% *vs* 52.2%), anaemia (35.0% *vs* 9.8%), nausea (31.9% *vs* 20.6%), diarrhoea (31.0% *vs* 29.7%), neutrophil count decreased (21.3% *vs* 2.1%) and fatigue (18.4% *vs* 20.8%). Among those EAEs, the frequencies were similar in the two treatment groups, except for neutropenia, anaemia, nausea and neutrophil count decreased with higher frequency in the S95005 + Bev group and palmar-plantar eythrodysaesthesia syndrome with lower frequency in the S95005 + Bev group (between-group difference > 5%).
The most frequent (> 5% in either treatment group) severe treatment-related EAEs were reported at higher frequency in the S95005 + Bev group for neutropenia (51.3% *vs* 1.4%), neutrophil count decreased (17.7% *vs* 0.7%), anaemia (10.6% *vs* 2.3%) and at lower frequency in the S95005 + Bev group for palmar-plantar erythrodysaesthesia syndrome (none vs 14.5%). Severe treatment-related diarrhoea was reported in 5.9% *vs* 4.2% and hypertension in 5.2% *vs* 7.5% of the patients respectively.

EAEs leading to study drug withdrawal were reported with a lower frequency in the S95005 + Bev group than in the Cap + Bev group: 25.8% *vs* 30.9%. These EAEs occurred in no more than 1% of patients except the following: malignant neoplasm progression (4.3% *vs* 4.0%), palmar-plantar erythrodysaesthesia syndrome (none *vs* 4.0%), asthenia and fatigue (1.7% *vs* 1.6% for each), general physical health deterioration (1.7% *vs* 0.9%), anaemia (1.2% *vs* none). Treatment-related EAEs leading to study drug withdrawal were reported for 11.6% of patients in the S95005 + Bev group and 15.9% in the Cap + Bev group. Severe EAEs leading to study drug withdrawal were reported for 17.5% *vs* 18.0%, respectively and serious EAEs leading to study drug withdrawal for 13.0% *vs* 13.8%, respectively.

EAEs led to cycle delayed were reported with a higher frequency in the S95005 + Bev group than in the Cap + Bev group: 75.9% *vs* 48.9%. The most common of these EAEs were neutropenia (54.8% *vs* 4.7%), neutrophil count decreased (17.3% *vs* 0.7%) and palmar-plantar eythrodysaesthesia syndrome (0.2% *vs* 16.4%). ***EAEs led to dose reduction*** were reported with a lower frequency in the S95005 + Bev group than in the Cap + Bev group: 18.8% *vs* 29.7%. The most common of these EAEs were neutropenia (8.3% *vs* 0.9%) and palmar-plantar eythrodysaesthesia syndrome (0.2% *vs* 17.3%).

COVID-19 infection was reported with a similar frequency in the two treatment groups: 25 patients (5.9%) in the S95005 + Bev *vs* 24 patients (5.6%) in the Cap + Bev group.

The percentage of patients who experienced ***serious EAE*** (including deaths as preferred term) was similar in the two groups: 41.6% in the S95005 + Bev group and 46.1% in the Cap + Bev group. The most frequent SEAEs
(≥ 5% in either group) were malignant neoplasm progression (4.5% in the S95005 + Bev group and 7.5% in the Cap + Bev group), pulmonary embolism at lower frequency in the S95005 + Bev group (2.4% *vs* 7.0%) and anaemia at higher frequency in the S95005 + Bev group (6.6% *vs* 1.6%). Other SEAEs reported for more than 2% of patients were deep vein thrombosis (1.7% in the S95005 + Bev group *vs* 3.5% in the Cap + Bev group), neutropenia (2.8% *vs* 0.2%), diarrhoea (2.6% *vs* 2.3%), febrile neutropenia (2.4% *vs* 0.5%), dehydration (2.1% *vs* 3.3%), intestinal obstruction (2.1% *vs* 1.4%), pneumonia (2.1% *vs* 1.2%).
Treatment-related SEAEs were reported for 19.6% of patients in the S95005 + Bev group and 22.5% in the Cap + Bev group. Treatment-related SEAEs occurred in less than 1% of patients except the following: anaemia (4.5% *vs* 1.2%), neutropenia (2.8% *vs* 0.2%), febrile neutropenia (2.1% *vs* 0.5%), pulmonary embolism (1.9% *vs* 4.4%), diarrhoea (1.9% *vs* 2.3%), deep vein thrombosis (0.9% *vs* 2.6%), dehydration (0.9% *vs* 2.1%).

Among on-study deaths, five occurred prior to any treatment intake for progressive disease. As of treated patients, deaths were reported for 40.7% in the S95005 + Bev group and 41.5% in the Cap + Bev group, including 10.4% and 10.1% who died during the treatment period. For patients who died during the follow-up period, the reason of death was mostly progressive disease: 85.2% *vs* 86.4% of deaths respectively. A total of 33 patients (7.8%) in the S95005 + Bev group and 41 patients (9.6%) in the Cap + Bev group experienced at least one EAE leading to death. For those patients, death occurred mostly during the treatment period (7.1% *vs* 9.1%). Treatment-related fatal EAEs were reported for 5 patients (1.2%) in the S95005 + Bev group patients and 4 patients (0.9%) in the Cap + Bev group as following:

- S95005 + Bev group: Dieulafoy's vascular malformation and gastric haemorrhage (both in a single patient), urosepsis (1 patient), pulmonary embolism and pulmonary haemorrhage (both in a single patient), cardiac failure chronic (1 patient), cardio-respiratory arrest (1 patient).

- Cap + Bev group: neutropenia, thrombocytopenia, lymphopenia, myelosuppression (these four events in a single patient), tumour haemorrhage (1 patient), tumour perforation and peritonitis (both in a single patient), vascular encephalopathy (1 patient).

Blood laboratory evaluation
For the biochemistry parameters, emergent severe abnormal values on treatment were sparse in the two treatment groups except for high GGT (8.5% in the S95005 + Bev group *vs* 4.3% in the Cap + Bev group, including 2.2% *vs* 0.5% Grade 4, respectively).
For the haematological parameters, emergent severe low neutrophils values on treatment were observed for 67.9% of patients in the S95005 + Bev group (including Grade 3 for 46.8% and Grade 4 for 21.1%) at higher frequency than in Cap + Bev group (3.1%). Treatment emergent severe abnormal low values for leukocytes, lymphocytes, platelets and low haemoglobin were also more frequent in the S95005 + Bev group than in the Cap + Bev group.

Other safety evaluation
There was no relevant difference between the two groups in mean changes for weight, blood pressure and heart rate.

In the FAS, the median time to worsening ECOG PS ≥ 2 was longer in the S95005 + Bev group than in the Cap + Bev group (13.5 *vs* 11.9 months) with no statistically significant difference.

CONCLUSION
This was an international, randomised, open-label, controlled two-arm, phase III study comparing S95005 in combination with bevacizumab (S95005 + Bev) to capecitabine in combination with bevacizumab (Cap + Bev) in the first-line treatment of patients with unresectable mCRC who were non-eligible for intensive therapy.

At the cut-off date, the primary analysis for Progression Free Survival (PFS) based on investigator assessment was performed on 628 PFS events among 856 randomised patients. Results did not demonstrate the statistically significant superiority of S95005 + Bev over Cap + Bev in reducing the risk of disease progression or death. The estimated hazard ratio (HR) was 0.87 (95% CI = [0.75; 1.02]) in favour of S95005 + Bev. The median PFS was 9.40 *vs* 9.26 months, respectively. The sensitivity analysis using PFS based on blind independent central review showed consistent results with HR of 0.85 (95% CI = [0.72, 1.00]), median PFS of 10.6 *vs* 9.3 months, respectively.

Quality of life was stable in the two treatment groups during the study.

The safety profile of S95005 in combination with bevacizumab in this study was in line with the one known both for S95005 as monotherapy or in combination with bevacizumab, characterised by hematologic and gastrointestinal as main emergent adverse events (EAE). Overall, severe (i.e. Grade ≥ 3) treatment-related EAEs were more frequent in the S95005 + Bev group than in the Cap + Bev group, mostly due to events related to myelosuppression, generally manageable. In the S95005 + Bev group, 65.5% of patients experienced treatment-related neutropenia (51.3% Grade ≥ 3), 35.0% anaemia (10.6% Grade ≥ 3) and 21.3% neutrophil count decreased (17.7% Grade ≥ 3) vs 8.4%, 9.8% and 2.1% (1.4%, 2.3% and 0.7% Grade ≥ 3 respectively) in the Cap + Bev group. Febrile neutropenia was reported for 2.4% the S95005 + Bev group and 0.5% in the Cap + Bev group, all serious and resolved. In the Cap + Bev group, the most frequent treatment-related EAE was palmar-plantar eythrodysaesthesia syndrome (52.2% *vs* 1.2% in the S95005 + Bev group; including 14.5% *vs* none Grade ≥ 3).
As regards of ECOG PS, the median time to worsening ECOG PS ≥ 2 was longer in the S95005 + Bev group than in the Cap + Bev group (13.5 *vs* 11.9 months) with no statistically significant difference.

This phase III study did not meet its primary objective which was to demonstrate the superiority of S95005 + Bev combination in PFS based as compared with Cap + Bev combination in first-line treatment of patients with unresectable metastatic colorectal cancer who were not candidate for intensive therapy.

Date of the report: 17 December 2021

Version of the report: Final Version