Clinical trial results:
A randomised, open-label, multi-centre, two-arm Phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a Safety Lead-In part in participants with KRAS/NRAS and BRAF wild type metastatic colorectal cancer previously treated with standard treatment and anti-EGFR therapy

Summary

EudraCT number	2021-003151-41
Trial protocol	DK BE FI HU PL
Global end of trial date	21 June 2023

Results information

Result version number	v1 (current)
This version publication date	25 January 2024
First version publication date	25 January 2024

Trial information

Trial identification

Sponsor protocol code	CL3-95026-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05223673
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2023
Global end of trial reached?	Yes
Global end of trial date	21 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety Lead-In part:
- Assessment of safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil according to National Cancer Institute Comment Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Phase III part:
- Compare overall survival (OS) of futuximab/modotuximab in combination with trifluridine/tipiracil versus trifluridine/tipiracil monotherapy in participants with tumours that are KRAS/NRAS and BRAF wild-type (WT) (Double negative). This phase III part did not start due to study discontinuation during the safety Lead-In part.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in 2013 in Fortaleza, with the GCP and with the applicable regulatory requirements. All the patients were to freely give their written informed consent before their selection in the study.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 April 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	7
EEA total number of subjects	5

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators were oncologists.

Pre-assignment

Screening details:

Participants must have histologically or cytologically confirmed adenocarcinoma of mCRC not amenable to surgical intervention. The participants must have received at least 2 prior regimens of standard chemotherapy and had demonstrated progressive disease or intolerance.

Period 1

Period 1 title	Treatment period in Safety Lead-in Part (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	futuximab/modotuximab + trifluridine/tipiracil

Arm description:

Patients received trifluridine/tipiracil in combination with futuximab/modotuximab

Arm type	Experimental
Investigational medicinal product name	trifluridine/tipiracil
Investigational medicinal product code	S95005
Other name	TAS-102; Lonsurf ®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trifluridine/tipiracil was administered, before futuximab/modotuximab administration, at a dose 35 mg/m²/dose, orally twice a day (BID), within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 14 days (2 weeks), followed by a 14-day (2 weeks) rest. This treatment cycle was repeated every 28-days (4 weeks).

Investigational medicinal product name	futuximab/modotuximab
Investigational medicinal product code	S95026
Other name	Sym004
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Futuximab/modotuximab was administered at a dose 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly beginning on C1D8 (maintenance doses) for all subsequent administrations, by intravenous (IV) infusion, after trifluridine/tipiracil intake. The first infusion on C1D1 (9 mg/kg in 500 mL) had to be administered over 1 hour. The maximum rate of infusion of 500 mL/hour should not be exceeded throughout the administration. Subsequent infusions (6 mg/kg in 250 mL) could be delivered over 30 minutes, maintaining the
maximum infusion rate of 500 mL/hour. Premedication for prophylaxis of infusion related reactions was mandatory prior to each dose of futuximab/modotuximab.

Number of subjects in period 1	futuximab/modotuximab + trifluridine/tipiracil
Started	7
Completed	0
Not completed	7
Adverse event, serious fatal	1
Progressive disease	6

Baseline characteristics

Reporting groups	
Reporting group title	futuximab/modotuximab + trifluridine/tipiracil
Reporting group description:	
Patients received trifluridine/tipiracil in combination with futuximab/modotuximab	

Reporting group values	futuximab/modotuximab + trifluridine/tipiracil	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	
From 65-84 years	6	6	
Age continuous Units: years			
arithmetic mean	67.3		
standard deviation	± 3.7	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	5	5	

End points

End points reporting groups

Reporting group title	futuximab/modotuximab + trifluridine/tipiracil
Reporting group description:	
Patients received trifluridine/tipiracil in combination with futuximab/modotuximab	

Primary: Safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil

End point title	Safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil[1]
End point description:	
All participants having taken at least one dose of IMP were included in Safety Set. No Dose Limiting Toxicity was reported.	
End point type	Primary
End point timeframe:	
Any AEs reported from the date of first administration of IMP to 30 days after the last date of IMP administration.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive summary statistics was applied to this end point

End point values	futuximab/modotuximab + trifluridine/tipiracil			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percent				
number (not applicable)				
Severe TEAEs	100			
Treatment-related TEAEs	100			
TEAE leading to trifluridine/tipiracil withdrawal	14.3			
TEAE leading to futuximab/modotuximab withdrawal	14.3			
Serious TEAEs	42.9			
Treatment-related serious TEAEs	0			
TEAE leading to death	14.3			
Treatment-related TEAE leading to death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAE) are defined as any AEs reported from the date of first administration of IMP to 30 days after the last date of IMP administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	futuximab/modotuximab + trifluridine/tipiracil

Reporting group description: -

Serious adverse events	futuximab/modotuximab + trifluridine/tipiracil		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice			

subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hyperventilation			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	futuximab/modotuximab + trifluridine/tipiracil		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Device related thrombosis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Fatigue subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 4		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Hyperventilation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Psychiatric disorders			

Confusional state			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Infusion related reaction			
subjects affected / exposed	4 / 7 (57.14%)		
occurrences (all)	4		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Taste disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Neutrophilia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 5 / 7 (71.43%) 11 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Ear and labyrinth disorders Tympanic membrane perforation subjects affected / exposed occurrences (all)	 1 / 7 (14.29%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth	 1 / 7 (14.29%) 1 2 / 7 (28.57%) 2 1 / 7 (14.29%) 1		

subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 7 (42.86%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	6 / 7 (85.71%)		
occurrences (all)	6		
Dry skin			
subjects affected / exposed	5 / 7 (71.43%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	2 / 7 (28.57%)		
occurrences (all)	2		
Onychoclasis			
subjects affected / exposed	1 / 7 (14.29%)		
occurrences (all)	1		

Pruritus subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all) Rash pruritic subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Renal and urinary disorders Nocturia subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Sacral pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2 1 / 7 (14.29%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Otitis externa subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 1 1 / 7 (14.29%) 2		

Paronychia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 3		
Tinea pedis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1		
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2		
Hypomagnesaemia subjects affected / exposed occurrences (all)	5 / 7 (71.43%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2022	Amendment No. 1 This substantial amendment incorporates changes requested by the health authorities (FDA and Belgium).
16 August 2022	Amendment No. 2 Text revised regarding management of skin toxicity globally per FDA feedback; Text was revised in Sections 8.11, 8.11.1, and 8.11.2, to provide more information about dose delay and specify maximum delay periods; Text was revised in Section 6.1 regarding COVID-19; Added timepoint in Section 9.6 and investigation schedule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 February 2023	During the Safety Lead-in part, the sponsor decided to discontinue the study for strategic reasons. This decision was not due to safety issue but to strategic consideration. The Phase III part was not started.	-

Notes:

Limitations and caveats

None reported