Clinical trial results:
An Open-label, Multiple-site, Phase I/II Dose Cohort Trial of [6R] 5,10-Methylene Tetrahydrofolate (Modufolin®) in Combination with a Fixed Dose of 5-Fluorouracil (5-FU) alone or together with a Fixed Dose of Oxaliplatin or Irinotecan in Patients with Stage IV Colorectal Cancer

Summary

EudraCT number	2014-001862-84
Trial protocol	SE NO DK GR
Global end of trial date	30 January 2020

Results information

Result version number	v1 (current)
This version publication date	14 February 2021
First version publication date	14 February 2021

Trial information

Trial identification

Sponsor protocol code	ISO-CC-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02244632
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Isofol Medical AB
Sponsor organisation address	Arvid Wallgrens Backe 20, Gothenburg, Sweden, SE-413 46
Public contact	Chief Medical Officer, Isofol Medical AB, +46 (0)31 7972280, info@isofolmedical.com
Scientific contact	Chief Scientific Officer, Isofol Medical AB, +46 (0)31 7972280, info@isofolmedical.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	25 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2020
Global end of trial reached?	Yes
Global end of trial date	30 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterise the tolerability of Modufolin in Stage IV CRC patients in 1st or 2nd line treatment in terms of toxicity during eight (8) weeks of treatment with one (1) of four (4) dose levels of Modufolin in the treatment arms.

Protection of trial subjects:

The study protocol and amendments were submitted to ethics committees and/or to competent authorities for approval before patients were recruited, in accordance with the International Council of Harmonisation guidelines, the applicable European Directives and local legal requirements. The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association. All patients received written and verbal information regarding the study, which emphasised that participation in the study was voluntary and that the patient could withdraw from the study at any time and for any reason. All patients were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study. Before performing any study-related procedures, the informed consent form was signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Sweden: 43
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Greece: 47
Worldwide total number of subjects	105
EEA total number of subjects	105

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)	48
From 65 to 84 years	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients ≥18 years with advanced metastatic colorectal (Stage IV) cancer and eligible for 1st or 2nd line therapy with evaluable disease with one measurable site of disease according to RECIST 1.1 criteria (at least 10 mm). Life expectancy ≥3 months, WHO performance status of 0-2 and adequate haematological, renal and hepatic function.

Period 1

Period 1 title	Main Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	30 mg/m2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	
Other name	Arfolitixorin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 30 mg/m2, intravenous injection	
Arm title	60 mg/m2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	
Other name	Arfolitixorin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 60 mg/m2, intravenous injection	
Arm title	120 mg/m2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	
Other name	Arfolitixorin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 120 mg/m2, intravenous injection	
Arm title	240 mg/m2

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	
Other name	Arfolitixorin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg/m2, intravenous injection

Number of subjects in period 1	30 mg/m2	60 mg/m2	120 mg/m2
Started	13	20	65
Completed	10	17	58
Not completed	3	3	7
Adverse event, serious fatal	-	1	2
Consent withdrawn by subject	1	-	3
Adverse event, non-fatal	1	1	-
Progression of disease	-	1	2
Need or requirement of alternative treatment	1	-	-

Number of subjects in period 1	240 mg/m2
Started	7
Completed	5
Not completed	2
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Progression of disease	2
Need or requirement of alternative treatment	-

Baseline characteristics

Reporting groups	
Reporting group title	Main Study

Reporting group description: -

Reporting group values	Main Study	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	63.6		
standard deviation	± 10.3	-	
Gender categorical Units: Subjects			
Female	50	50	
Male	55	55	

End points

End points reporting groups

Reporting group title	30 mg/m2
Reporting group description: -	
Reporting group title	60 mg/m2
Reporting group description: -	
Reporting group title	120 mg/m2
Reporting group description: -	
Reporting group title	240 mg/m2
Reporting group description: -	

Primary: Number and severity of dose limiting toxicity

End point title	Number and severity of dose limiting toxicity[1]

End point description:

End point type	Primary

End point timeframe:

During 4 cycles of treatment with IMP (8 weeks in total).

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: This was a safety study and no formal statistical testing was performed.

End point values	30 mg/m2	60 mg/m2	120 mg/m2	240 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	20	65	7
Units: number				
Total	8	17	59	2
Grade 1	0	2	9	0
Grade 2	2	6	23	0
Grade 3	2	7	24	2
Grade 4	4	2	2	0
Grade 5	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate

End point title	Objective Response Rate[2]

End point description:

Only patients alive and without major protocol deviations after 8 weeks are included (per protocol set).

End point type	Primary

End point timeframe:

Number of patients with response after 4 treatment cycles (8 weeks of treatment).

Notes:

[2] - 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: This was a safety study and no formal statistical testing was performed.

End point values	30 mg/m2	60 mg/m2	120 mg/m2	240 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	14	55	5
Units: patients				
Responders	0	4	13	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During 4 cycles of treatment with IMP (8 weeks in total).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Overall Main Study

Reporting group description: -

Serious adverse events	Overall Main Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 105 (21.90%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 105 (2.86%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			

subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Proctalgia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Perirectal abscess			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Main Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 105 (81.90%)		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	15 / 105 (14.29%)		
occurrences (all)	27		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 105 (9.52%)		
occurrences (all)	15		
Neutropenia			
subjects affected / exposed	20 / 105 (19.05%)		
occurrences (all)	30		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 105 (28.57%)		
occurrences (all)	40		
Mucosal inflammation			

subjects affected / exposed	9 / 105 (8.57%)		
occurrences (all)	10		
Pyrexia			
subjects affected / exposed	13 / 105 (12.38%)		
occurrences (all)	16		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 105 (9.52%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	26 / 105 (24.76%)		
occurrences (all)	39		
Nausea			
subjects affected / exposed	31 / 105 (29.52%)		
occurrences (all)	55		
Vomiting			
subjects affected / exposed	17 / 105 (16.19%)		
occurrences (all)	33		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 105 (8.57%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2014	Amendment to the study protocol and IB based on input from the Swedish regulatory authority MPA. Changes were made to the study rationale, design as well as safety evaluation and reporting.
21 January 2015	Inclusion of Denmark and Norway. Introduction om Arm #3 (Irinotecan treatment). Removal of arfolitixorin dose 120 mg/m2 in Treatment Arm #1. Addition of explorative endpoint tissue sample for gene expression.
17 June 2015	Introduced a sub-study, the Follow-up Study, which would allow the continued treatment with arfolitixorin in those patients who did not show either clinical or radiological signs of disease progression after completing the study treatment in the initial 8 week treatment (i.e., Main Study). Further adaptation of the method for assigning patients to treatment to ensure that patients deemed fit for at least one of the chemotherapies in the treatment arms could enrol even if unfit for the other treatment arms in the study. Changes in the eligibility criteria for enrolment in the Main Study, such as changes to align with the adaptation of the method for allocation of patients to treatments, and to allow patients in other than first line settings.
22 April 2016	Introduced new treatment cohorts with higher arfolitixorin doses (i.e., 120 and 240 mg/m2) with the aim to acquire information critical for the design of planned next clinical study with arfolitixorin in the intended indication. Adaptation of the requirements needed to ensure that data collected was satisfactory for a suitable assessment of the tolerability of arfolitixorin in the combination with the chemotherapies given. The assessment of dU levels was re-classified as an exploratory endpoint (previously secondary efficacy endpoint).
03 October 2016	Introduced a new chemotherapy infusion regimen and a treatment arm including bevacizumab. The primary endpoint was updated to clarify that, not only the number of patients who had their chemotherapy dose adjusted due to related toxicity, but also the actual number of dose adjustments made would be assessed. Greece was also included for recruitment of patients in several clinical sites. The eligibility criteria for enrolment in the Main Study were updated in alignment with introduction of the new treatment arms and applicable clinical practice. The contact information for the new Coordinating Investigator, as notified separately (15-Jun-2016), was updated.
05 July 2017	Introduced new treatment cohorts in Treatment Arm #5 leading to administration of up to three (3) doses of the IMP: 60 mg/m2, 120 mg/m2 and 240 mg/m2 instead of only receiving arfolitixorin at the SP2D.
23 November 2017	Up to 10 new patients were planned to be included in each of Treatment Arm #4 and #6, respectively. All new patients added received arfolitixorin at the SP2D. Addition of a tumour biomarker blood sample collection for patients in Treatment Arm #4 and #6, respectively. Addition of nine (9) patients at the SP2D in Treatment Arm #5.

19 July 2018	Included the expansion of Cohort #18 (Treatment Arm #4) and the cohort(s) in the Treatment Arm #6 with additional 10 patients in each treatment regimen, i.e. 20 new patients in the clinical study. With this amendment the Sponsor aimed to obtain more data on the safety, tolerability, and efficacy. Included the statement that the amended study protocol is in accordance with the then newly enforced General Data Protection Regulation (GDPR).
22 November 2019	Changes were made to the eligibility (exclusion criteria #2 and #16) for enrolment in the Main Study. Change to the secondary objective regarding evaluation of tumour response and disease progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported