



Clinical trial results:

An Open-Label, Multicenter, Phase I/II Clinical Trial to Identify the Modufolin® Dose with Most Favorable Safety Prospect and Confirmed Ability to Mitigate High-Dose Methotrexate Induced Toxicity during Treatment of Osteosarcoma Patients

Summary

EudraCT number	2013-001280-23
Trial protocol	SE HU CZ
Global end of trial date	03 January 2017

Results information

Result version number	v1 (current)
This version publication date	29 November 2018
First version publication date	29 November 2018

Trial information

Trial identification

Sponsor protocol code	ISO-MTX-003
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987102
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Isofol Medical AB
Sponsor organisation address	Biotech Center, Arvid Wallgrens backe 20, Gothenburg, Sweden, SE.413 46
Public contact	Principal Investigator, Skåne University Hospital, +46 (0)46177507, mikael.eriksson@med.lu.se
Scientific contact	Chief Medical Officer, Isofol Medical AB, +46 (0)702433750, karin.ganlov@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	22 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2017
Global end of trial reached?	Yes
Global end of trial date	03 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To characterize safety in terms of toxicity during HDMTX treatment and folate rescue therapy with either Modufolin® or Calcium Folate.
- To identify the recommended dose of Modufolin® for further assessment.

Protection of trial subjects:

During HDMTX treatment cycles patients were given a restricted diet and beverage intake in order to avoid any unwanted effect in kidney function or hydration schedules which may result in delays in MTX elimination.

Vitamin B supplements or other intake rich in folates were not be permitted during patient participation in the study.

Urinary pH was monitored and had to be ≥ 7 , before the start of the MTX infusion had to be maintained above 7 until S-MTX was $\leq 0.1 \mu\text{mol/L}$.

Contrast radiography, e.g. computerized tomography (CT) and phlebography, was avoided the days prior and during HDMTX treatment as contrast media may injure the kidneys.

Voraxaze (Glucarpidase G2) was to be considered in case of excessively high MTX levels in accordance with the MTX-toxicity management instructions established for this study.

Background therapy:

A full planned MAP treatment regimen comprised six 5-week cycles of chemotherapy with surgical resection of the tumor at the discretion of the investigator.

Each cycle of MAP included 1 course of adriamycin/doxorubicin (75 mg/m²) and cisplatin (120 mg/m²) at week 1.

Each cycle of MAP included 2 consecutive courses of high-dose methotrexate (HDMTX) (12 g/m²) at week 4 and week 5.

In general the completion of a full MAP treatment regimen takes between 6 to 10 months.

Evidence for comparator: -

Actual start date of recruitment	02 September 2013
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	Poland: 3
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	1
Adolescents (12-17 years)	13
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients were pre-screened by the Principal Investigator (PI) or designated Investigator(s) among those patients who have received confirmed diagnosis of osteosarcoma and were planned for surgical resection of the tumor in combination with neoadjuvant or adjuvant chemotherapy.

Pre-assignment

Screening details:

Males and females, 12 to 40 years, with histological evidence of osteosarcoma (metastatic osteosarcoma accepted) and eligible for continued HDMTX treatment after receiving the 2 first adjacent courses of HDMTX with Calcium Folate rescue in accordance with the specified MAP regimen.

Pre-assignment period milestones

Number of subjects started	18
Number of subjects completed	18

Period 1

Period 1 title	2 courses of HDMTX with SOC rescue
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (15 mg/m2 Modufolin)

Arm description:

2 courses of HDMTX with Modufolin (MOD) rescue (15 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue

Arm type	Experimental
Investigational medicinal product name	Calcium folinate
Investigational medicinal product code	V03AF03
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administration of SOC will start 24 h after HDMTX administration and then q6h until serum levels of MTX is less or equal to 0.1 microM.

Arm title	Cohort 2 (7.5 mg/m2 Modufolin)
------------------	--------------------------------

Arm description:

2 courses of HDMTX with Modufolin (MOD) rescue (7.5 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue

Arm type	Experimental
Investigational medicinal product name	Calcium folinate
Investigational medicinal product code	V03AF03
Other name	N/A
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administration of SOC will start 24 h after HDMTX administration and then q6h until serum levels of MTX is less or equal to 0.1 microM.

Number of subjects in period 1	Cohort 1 (15 mg/m ² Modufolin)	Cohort 2 (7.5 mg/m ² Modufolin)
Started	8	10
Completed	4	4
Not completed	4	6
Adverse event, non-fatal	2	2
Incorrectly included	-	1
Change in planned chemotherapy	1	-
Laboratory abnormality	1	2
Protocol deviation	-	1

Period 2

Period 2 title	2 courses of HDMTX with MOD rescue
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (15 mg/m ² Modufolin)

Arm description:

2 courses of HDMTX with Modufolin (MOD) rescue (15 mg/m²) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue

Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administration of MOD will start 24 h after HDMTX administration and then q6h until serum levels of MTX is less or equal to 0.1 microM.

Arm title	Cohort 2 (7.5 mg/m ² Modufolin)
------------------	--

Arm description:

2 courses of HDMTX with Modufolin (MOD) rescue (7.5 mg/m²) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue

Arm type	Experimental
Investigational medicinal product name	Modufolin
Investigational medicinal product code	N/A
Other name	N/A
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Administration of MOD will start 24 h after HDMTX administration and then q6h until serum levels of MTX is less or equal to 0.1 microM.

Number of subjects in period 2	Cohort 1 (15 mg/m ² Modufolin)	Cohort 2 (7.5 mg/m ² Modufolin)
Started	4	4
Completed	4	3
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 (15 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (15 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	
Reporting group title	Cohort 2 (7.5 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (7.5 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	

Reporting group values	Cohort 1 (15 mg/m2 Modufolin)	Cohort 2 (7.5 mg/m2 Modufolin)	Total
Number of subjects	8	10	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	1	1
Adolescents (12-17 years)	7	6	13
Adults (18-64 years)	1	3	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	2	3
Male	7	8	15

Subject analysis sets

Subject analysis set title	APTS
Subject analysis set type	Safety analysis
Subject analysis set description: The All Patients Treated Set (APTS) included all patients receiving at least one bolus injection of Modufolin.	

Reporting group values	APTS		
Number of subjects	8		
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)	7		
Adults (18-64 years)	1		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	0		
Male	8		

End points

End points reporting groups

Reporting group title	Cohort 1 (15 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (15 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	
Reporting group title	Cohort 2 (7.5 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (7.5 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	
Reporting group title	Cohort 1 (15 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (15 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	
Reporting group title	Cohort 2 (7.5 mg/m2 Modufolin)
Reporting group description: 2 courses of HDMTX with Modufolin (MOD) rescue (7.5 mg/m2) after completed 2 courses of HDMTX with SOC (Calcium Folate) rescue	
Subject analysis set title	APTS
Subject analysis set type	Safety analysis
Subject analysis set description: The All Patients Treated Set (APTS) included all patients receiving at least one bolus injection of Modufolin.	

Primary: Number of AEs per severity (ALL)

End point title	Number of AEs per severity (ALL) ^[1]
End point description: Results for the two cohorts are presented for APTS. NCI CTCAE v4.0 was used for assessment of severity.	
End point type	Primary
End point timeframe: From the start of HDMTX administration through 8 days post dose for each course of HDMTX.	

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: Data was summarized for APTS (all and per cohort). No statistical significance testing was performed due to few patients in each cohort.

End point values	Cohort 1 (15 mg/m2 Modufolin)	Cohort 2 (7.5 mg/m2 Modufolin)	APTS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	8	
Units: number				
Grade 1	40	27	67	
Grade 2	8	15	23	
Grade 3	11	6	17	
Grade 4	3	1	4	

Statistical analyses

No statistical analyses for this end point

Primary: Number of HDMTX related AEs per severity (ALL)

End point title	Number of HDMTX related AEs per severity (ALL) ^[2]
-----------------	---

End point description:

Results for the two cohorts are presented for APTS.
NCI CTCAE v4.0 was used for assessment of severity.

End point type	Primary
----------------	---------

End point timeframe:

From the start of HDMTX administration through 8 days post dose for each course of HDMTX.

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: Data was summarized for APTS (all and per cohort). No statistical significance testing was performed due to few patients in each cohort.

End point values	Cohort 1 (15 mg/m2 Modufolin)	Cohort 2 (7.5 mg/m2 Modufolin)	APTS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	8	
Units: number				
Grade 1	25	20	45	
Grade 2	6	12	18	
Grade 3	6	5	11	
Grade 4	1	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of ongoing AEs (ALL) per HDMTX course

End point title	Number of ongoing AEs (ALL) per HDMTX course ^[3]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

From the start of HDMTX administration through 8 days post dose for each course of HDMTX.

Notes:

[3] - 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: Data was summarized for APTS (all and per cohort). No statistical significance testing was performed due to few patients in each cohort.

End point values	Cohort 1 (15 mg/m2 Modufolin)	Cohort 2 (7.5 mg/m2 Modufolin)	APTS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	8	
Units: number				
Course 1 (SOC)	14	10	24	
Course 2 (SOC)	19	10	29	

Course 1 (MOD)	6	10	16	
Course 2 (MOD)	14	16	30	

Statistical analyses

No statistical analyses for this end point

Primary: Number of ongoing HDMTX related AEs per HDMTX course

End point title	Number of ongoing HDMTX related AEs per HDMTX course ^[4]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

From the start of HDMTX administration through 8 days post dose for each course of HDMTX.

Notes:

[4] - 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: Data was summarized for APTS (all and per cohort). No statistical significance testing was performed due to few patients in each cohort.

End point values	Cohort 1 (15 mg/m ² Modufolin)	Cohort 2 (7.5 mg/m ² Modufolin)	APTS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	4	4	8	
Units: number				
Course 1 (SOC)	13	8	21	
Course 2 (SOC)	13	8	21	
Course 1 (MOD)	5	10	15	
Course 2 (MOD)	12	16	28	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of HDMTX administration through 8 days post dose for each course of HDMTX.

Adverse event reporting additional description:

The AEs are presented for the APTS as these patients have been exposed to MOD.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

Reporting groups

Reporting group title	Cohort 1 (15 mg/m2 Modufolin)
-----------------------	-------------------------------

Reporting group description:

HDMTX rescue using Modufolin (15 mg/m2)

Reporting group title	Cohort 2 (7.5 mg/m2 Modufolin)
-----------------------	--------------------------------

Reporting group description:

HDMTX rescue using Modufolin (7.5 mg/m2)

Serious adverse events	Cohort 1 (15 mg/m2 Modufolin)	Cohort 2 (7.5 mg/m2 Modufolin)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Candida sepsis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1 (15 mg/m ² Modufolin)	Cohort 2 (7.5 mg/m ² Modufolin)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	
occurrences (all)	8	3	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	
occurrences (all)	7	2	
Drug clearance decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Platelet count decreased			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	1 / 4 (25.00%) 1	
Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	1 / 4 (25.00%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 9	0 / 4 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	
General disorders and administration site conditions Localised oedema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 4 (50.00%) 3	
Pyrexia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 4 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 4	0 / 4 (0.00%) 0	
Nausea			

subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	3 / 4 (75.00%) 7	
Stomatitis subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	2 / 4 (50.00%) 4	
Vomiting subjects affected / exposed occurrences (all)	4 / 4 (100.00%) 14	4 / 4 (100.00%) 13	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	
Epistaxis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
Renal and urinary disorders Nephropathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
Infections and infestations Bacterial disease carrier subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
Cheilitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 3	
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2013	<p>The sponsor had become aware of a possible future change of the MTX-analysis method at some local laboratories participating in the study. In order to secure the quality of the data for endpoint analysis the sponsor introduced duplicate samplings for MTX analysis in the protocol. The back-up samples were frozen and kept for central analysis in case an up-dated analytical method could be suspected to have had a negative impact on the quality of the analysis results at any site during the conduct of the study. If there was no need for central analysis, the back-up samples would be destroyed after study completion.</p> <p>In addition to the above substantial changes some changes of administrative character and corrections of typographical errors were also made.</p>
20 June 2014	<p>Due to slow recruitment of study patients two sites in the Czech Republic were added and the study period was prolonged until Q1 2015.</p> <p>Adequate methods of contraception were described in detail.</p> <p>This was a non-substantial amendment.</p>
11 December 2014	<ul style="list-style-type: none">- Clarified and completed the definitions of population analysis sets- Specified that not all clinic sites would collect blood samples for the folate pharmacokinetic (PK) analysis due to administrative reasons- Clarified definitions and descriptions of certain specified study procedures- Included a number of non-substantial changes of minor importance for the study performance
27 August 2015	<ul style="list-style-type: none">- Allowed the age group 6 to 11 years to take part in the study in Cohort 2, in case the DSMB assessment of the clinical data collected during Cohort 1 could support a recommendation for enrollment of these younger patients without risking their safety. The opinion of the DSMB was that children in the age group six (6) to 11 years (both included) would not present PK or PD profiles different from that seen in children aged 12 years old. Thus the safety monitoring currently implemented in the study was considered satisfactory to guarantee the safety of enrolled patients even at a lower age limit (i.e. 6 years instead of 12). Upon completion of Cohort 1, the DSMB will convene and assess the clinical data collected until that time-point to give a recommendation for enrolment age that ensures that the safety of younger children will not be put at risk during the execution of Cohort 2. This change was made to allow the collection of safety data in these younger patients and to facilitate patient enrollment in the present study.- Included changes in the responsibilities of the DSMB- Amended the timelines for serious adverse event reporting to avoid unnecessary reporting prior to dosing of the study specific treatment- Updated administrative information- Included a number of non-substantial changes of minor importance for the study performance
04 February 2016	<ul style="list-style-type: none">- Allowed the number of patients treated with Modufolin (MOD) to be increased with 3 additional evaluable patients exposed to MOD in the dose recommended by the DSMB for future development. This change was added to generate additional safety data for the recommended dose before continuing with the pivotal study.- Included an update of the COG management recommendations during MOD rescue allowing a dosing frequency of q3h in case of Grade B toxicities. This that was supported by findings from this study and safety data collected from 45 patients with colorectal carcinoma exposed to MOD in clinical trials.- Adapted the blood sampling time points to clinical practice although this change lead to rescue treatments initiated before the analytical results were available.- Removed MTX back-up samples aimed for central analysis as such results would not contribute or influence the clinical treatment decisions based on locally analyzed MTX values available in real time.- Included a number of non-substantial changes of minor importance for the study performance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported