Clinical trial results:
A single arm study in metastatic colorectal cancer patients treated with pharmacokinetically (PK) dose adjusted weekly or biweekly 5-fluorouracil (5-FU) regimes.

Summary

EudraCT number	2011-003553-26
Trial protocol	DE
Global end of trial date	17 September 2014

Results information

Result version number	v1 (current)
This version publication date	05 September 2018
First version publication date	05 September 2018

Trial information

Trial identification

Sponsor protocol code	C-II-009

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CESAR Central European Society for Anticancer Drug Research-EWIV
Sponsor organisation address	Hanglüssgasse, 4/1-3, Vienna, Austria, 1150
Public contact	Sponsor, CESAR Central European Society for Anticancer Drug Research-EWIV , 0043 1522309316, max.roessler@cesar.or.at
Scientific contact	Sponsor, CESAR Central European Society for Anticancer Drug Research-EWIV , 0043 6765273814, max.roessler@cesar.or.at

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	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2014
Global end of trial reached?	Yes
Global end of trial date	17 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable intrapatient dose level of 20-30 mg.h /l. The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application versus the fourth application.

Protection of trial subjects:

Patients within this trial receive pharmacokinetically adapted 5-FU infusions. Beside the individual dose adaptation, which requires additional blood draws, patients are treated according to clinical routine. In order to further reduce interventions, the needle punctures required for PK-assessments were performed in course of routine blood draws.
Safety measures like regular blood analysis were performed according to clinical routine.

Background therapy:

n.a.

Evidence for comparator:

n.a.

Actual start date of recruitment	13 July 2012
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	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	32
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

7 study sites in Germany participated in the study. Recruitment started on 13.07.2012 and ended at 10.07.2014 as the last patient was recruited.

Pre-assignment

Screening details:

The screening criteria were defined by the inclusion and exclusion criteria as defined in the study protocol.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n.a.

Arms

Arm title	Experimental Treatment Arm

Arm description:

Patients will be treated with AIO-regime (weekly), FUFOX-regime (weekly) or FOLFOX-6 regime (bi-weekly). Patients will be dosed for the first time in accordance to established local standard and then 5-FU will be individually adjusted before every chemotherapy application, beginning with the second application. Dose adjustments for 5-FU will be either calculated according to toxicity and/or to the results of plasma concentrations from the preceding application (see algorithm below). Patients will remain on study until a total of 6 doses of FU-treatment have been administered and the end-of-treatment visit has been performed (weekly regimen: 9 weeks and bi-weekly regimen 13 weeks) or until withdrawal of patient`s consent, or withdrawal by the treating physician for safety reasons or due tumor progression, whatever comes first.
Following study completion, patients will receive further treatment according to best local practice.

Arm type	Experimental
Investigational medicinal product name	5-Fluoruracil
Investigational medicinal product code	L01BC02
Other name	5-Fluor-1H-pyrimidin-2,4-dion
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration according to SmPC. Individual dosing according to dosing algorithm outlined in CSP.

Number of subjects in period 1	Experimental Treatment Arm
Started	75
Completed	75

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	75	75	
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			
Age continuous			
Units: years			
arithmetic mean	65.06		
standard deviation	± 10.8	-	
Gender categorical Units: Subjects			
Female	32	32	
Male	43	43	

Subject analysis sets

Subject analysis set title	ITT-AIO Week-2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP at week 2.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FUFOX-Week2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FUFOX regime) at week 2.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FOLFOX6 Week 3
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FOLFOX-6 regime) at week 3.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-AIO Week-5
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP at week 5.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FUFOX-Week5
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FUFOX regime) at week 5.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FOLFOX6 Week 9
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FOLFOX-6 regime) at week 9.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Reporting group values	ITT-AIO Week-2	ITT-FUFOX-Week2	ITT-FOLFOX6 Week 3
Number of subjects	16	33	26
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age continuous			
Units: years			
arithmetic mean	71,77	60,84	66,29
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female	32		
Male	43		

Reporting group values	ITT-AIO Week-5	ITT-FUFOX-Week5	ITT-FOLFOX6 Week 9
Number of subjects	16	33	26
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age continuous			
Units: years arithmetic mean standard deviation	 71,77 ±	 60,84 ±	 66,29 ±
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Experimental Treatment Arm

Reporting group description:

Patients will be treated with AIO-regime (weekly), FUFOX-regime (weekly) or FOLFOX-6 regime (bi-weekly). Patients will be dosed for the first time in accordance to established local standard and then 5-FU will be individually adjusted before every chemotherapy application, beginning with the second application. Dose adjustments for 5-FU will be either calculated according to toxicity and/or to the results of plasma concentrations from the preceding application (see algorithm below). Patients will remain on study until a total of 6 doses of FU-treatment have been administered and the end-of-treatment visit has been performed (weekly regimen: 9 weeks and bi-weekly regimen 13 weeks) or until withdrawal of patient`s consent, or withdrawal by the treating physician for safety reasons or due tumor progression, whatever comes first.
Following study completion, patients will receive further treatment according to best local practice.

Subject analysis set title	ITT-AIO Week-2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP at week 2.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FUFOX-Week2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FUFOX regime) at week 2.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FOLFOX6 Week 3
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FOLFOX-6 regime) at week 3.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-AIO Week-5
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP at week 5.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FUFOX-Week5
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FUFOX regime) at week 5.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Subject analysis set title	ITT-FOLFOX6 Week 9
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patient in the ITT group who reveived IMP (FOLFOX-6 regime) at week 9.
The Intent-to-Treat (ITT) population was defined as all enrolled patients with at least one 5-FU treatment. It was the primary analysis population for safety and efficacy analysis.

Primary: Primary Endpoint in AIO ITT Patients

End point title	Primary Endpoint in AIO ITT Patients

End point description:

To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable intrapatient dose level of 20-30 mg.h /l.The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application versus the fourth application.

End point type	Primary

End point timeframe:

First 5-FU application till fourth 5 FU application

End point values	Experimental Treatment Arm	ITT-AIO Week-2	ITT-AIO Week-5	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	16	16	
Units: Patients	16	16	16	

Statistical analyses

Statistical analysis title	McNemar’s test

Statistical analysis description:

The primary endpoint was the comparison between the proportion of patients with an AUC in target range during the first 5-FU application versus the fourth 5-FU application.
This comparison was performed with a McNemar’s test to determine whether the row and column marginal frequencies (in a 2x2 contingency table of the first vs. fourth application vs. within target range vs. not within target range) were equal.

Comparison groups	ITT-AIO Week-2 v ITT-AIO Week-5
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.5637
Method	Mcnemar

Notes:

[1] - McNemar’s test to determine whether the row and column marginal frequencies (in a 2x2 contingency table of the first vs. fourth application vs. within target range vs. not within target range) were equal.

Primary: Primary Endpoint in FUFOX ITT Patients

End point title	Primary Endpoint in FUFOX ITT Patients

End point description:

End point type	Primary

End point timeframe:

Between 1st and Fourth study drug administration

End point values	ITT-FUFOX-Week2	ITT-FUFOX-Week5		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	33		
Units: Patients	28	27		

Statistical analyses

Statistical analysis title	McNemar’s test
Comparison groups	ITT-FUFOX-Week2 v ITT-FUFOX-Week5
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1336
Method	Mcnemar

Primary: Primary Endpoint in FOLFOX-6 ITT Patients

End point title	Primary Endpoint in FOLFOX-6 ITT Patients

End point description:

End point type	Primary

End point timeframe:

First to fourth application

End point values	ITT-FOLFOX6 Week 3	ITT-FOLFOX6 Week 9		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: Patients	24	22		

Statistical analyses

Statistical analysis title	McNemar’s test
Comparison groups	ITT-FOLFOX6 Week 9 v ITT-FOLFOX6 Week 3
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0209
Method	Mcnemar

Notes:

[2] - McNemar’s test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs have been assessed from first study drug administration to the End of treatment visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	AIO (weekly)

Reporting group description:

AIO-Regimen:
5-FU 2600 mg/m². Infusion for 24 hours. Leucovorin 200 mg/m²
Once weekly for 6 weeks, 2 weeks off.
Continuous intravenous infusion of 5-FU for 24 hours given as a continuous infusion. Additionally the regimen can contain oxaliplatin.
Either bevacizumab or cetuximab may be added to the regimens, according to local medical practice at each center.

Reporting group title	FUFOX (weekly)

Reporting group description:

FUFOX:
Oxaliplatin 60mg/m² . Infusion for 2 (-6) hours.
5FU 2000 mg/m². Infusion for 24 hours. Leucovorin 200 mg/m²
Once weekly for 6 weeks, 2 weeks off
Continuous intravenous infusion of 5-FU for 24 hours given as a continuous infusion. Additionally the regimen can contain oxaliplatin.
Either bevacizumab or cetuximab may be added to the regimens, according to local medical practice at each center.

Reporting group title	FOLFOX6 (bi-weekly)

Reporting group description:

Modified FOLFOX6:
Oxaliplatin 85 mg/m² as Infusion for 2 (-6) hours.
5-FU 400 mg/m² on day 1 as bolus (OPTIONAL)
5-FU 2400 mg/m² Infusion for 46 hours.
Leucovorin 400 mg or 400mg/m2 (the same dosing scheme should consistently be used for a patient)
Repeat every 2 weeks.
Either bevacizumab or cetuximab may be added to the regimen, according to local medical practice at each center.

Serious adverse events	AIO (weekly)	FUFOX (weekly)	FOLFOX6 (bi-weekly)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	13 / 33 (39.39%)	5 / 26 (19.23%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events	2	1	1
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ulcerative keratitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	5 / 33 (15.15%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal fistula			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 16 (6.25%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vomiting			

subjects affected / exposed	0 / 16 (0.00%)	3 / 33 (9.09%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida sepsis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Device related infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			

subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic encephalopathy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 16 (0.00%)	3 / 33 (9.09%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AIO (weekly)	FUFOX (weekly)	FOLFOX6 (bi-weekly)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 16 (87.50%)	32 / 33 (96.97%)	26 / 26 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Thrombosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Venous thrombosis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	3 / 33 (9.09%)	1 / 26 (3.85%)
occurrences (all)	1	3	1
Catheter site pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Chest discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	1 / 16 (6.25%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Discomfort			

subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	4 / 16 (25.00%)	10 / 33 (30.30%)	9 / 26 (34.62%)
occurrences (all)	4	10	9
Mucosal dryness			
subjects affected / exposed	1 / 16 (6.25%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
General physical health deterioration			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Impaired healing			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	5 / 26 (19.23%)
occurrences (all)	0	2	5
Needle issue			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	4 / 33 (12.12%)	5 / 26 (19.23%)
occurrences (all)	0	4	6
Swelling			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Temperature intolerance			

subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Drug hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Epistaxis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	5 / 26 (19.23%)
occurrences (all)	0	1	5
Oropharyngeal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Sleep disorder			

subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Blood magnesium increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Blood urine present			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Platelet count increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Protein total decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
White blood cell count decreased			

subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Dysgeusia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 33 (3.03%)	2 / 26 (7.69%)
occurrences (all)	1	1	2
Headache			
subjects affected / exposed	1 / 16 (6.25%)	1 / 33 (3.03%)	3 / 26 (11.54%)
occurrences (all)	1	1	3
Mononeuropathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	9 / 33 (27.27%)	5 / 26 (19.23%)
occurrences (all)	0	9	5
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 16 (0.00%)	6 / 33 (18.18%)	4 / 26 (15.38%)
occurrences (all)	0	6	4
Polyneuropathy			

subjects affected / exposed	0 / 16 (0.00%)	10 / 33 (30.30%)	5 / 26 (19.23%)
occurrences (all)	0	10	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	1 / 33 (3.03%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Granulocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Neutropenia			
subjects affected / exposed	0 / 16 (0.00%)	3 / 33 (9.09%)	2 / 26 (7.69%)
occurrences (all)	0	3	2
Thrombocytopenia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Intraocular haematoma			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	2 / 33 (6.06%)	3 / 26 (11.54%)
occurrences (all)	1	2	3
Abdominal pain upper			
subjects affected / exposed	1 / 16 (6.25%)	2 / 33 (6.06%)	2 / 26 (7.69%)
occurrences (all)	1	2	2
chapped lips			

subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	9 / 33 (27.27%)	6 / 26 (23.08%)
occurrences (all)	0	9	6
Diarrhoea			
subjects affected / exposed	8 / 16 (50.00%)	17 / 33 (51.52%)	6 / 26 (23.08%)
occurrences (all)	11	24	7
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	3 / 26 (11.54%)
occurrences (all)	0	1	3
Dysphagia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Eructation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	7 / 16 (43.75%)	21 / 33 (63.64%)	9 / 26 (34.62%)
occurrences (all)	9	29	10
Oesophagitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	1 / 16 (6.25%)	5 / 33 (15.15%)	2 / 26 (7.69%)
occurrences (all)	1	5	2
Vomiting			
subjects affected / exposed	5 / 16 (31.25%)	12 / 33 (36.36%)	7 / 26 (26.92%)
occurrences (all)	6	16	7
Abdominal distension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Abdominal rigidity			

subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Glossodynia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	5 / 26 (19.23%)
occurrences (all)	0	0	5
Dermatitis acneiform			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Dry skin			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Night sweats			

subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	2 / 26 (7.69%)
occurrences (all)	0	1	2
Rash			
subjects affected / exposed	1 / 16 (6.25%)	5 / 33 (15.15%)	3 / 26 (11.54%)
occurrences (all)	1	5	4
Urticaria			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Postrenal failure			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Muscle spasms			

subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Clostridium difficile colitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Erysipelas			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	4 / 33 (12.12%)	0 / 26 (0.00%)
occurrences (all)	0	4	0

Oesophageal candidiasis			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Oral herpes			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Paronychia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Purulence			
subjects affected / exposed	0 / 16 (0.00%)	1 / 33 (3.03%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	1 / 26 (3.85%)
occurrences (all)	0	2	2
Neutrophil count decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 33 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 16 (18.75%)	11 / 33 (33.33%)	6 / 26 (23.08%)
occurrences (all)	4	11	6
Dehydration			
subjects affected / exposed	0 / 16 (0.00%)	2 / 33 (6.06%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	0 / 16 (0.00%)	4 / 33 (12.12%)	3 / 26 (11.54%)
occurrences (all)	0	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2012	Changes to better reflect patient populations in clinical routine and corrective changes: 1) Inclusion criteria 10 and 12 were changed into: Patients show a sufficient hepatic and renal function to undergo 5-FU or 5-FU combination treatment, based on the investigators' discretion and in accordance to the recommendation outlined in the SmPCs. 2) New inclusion criteria: Patients being naïve to 5-FU treatment or having received a maximum of only one treatment cycle of 5-FU without experiencing any AEs/SAEs related to the study drug. 3) The AUC limits were corrected in the tables of sections 1.4.2 and 5.1.2. 4) Wording of Primary objective was amended to take into account the changed inclusion criteria: To determine whether pharmacokinetically-guided dose adjustment of 5-FU provides a stable intrapatient dose level of 20-30 mg.h /l. The primary analysis will be the comparison of the proportion of patients with AUC within 20 to 30 mg.h/L after the first 5-FU application within the study versus the fourth application within the study. 5) The use of Leucovorin in the dosage 400mg/m² was allowed. 6) In case no 5-FU plasma concentration has been measured or no valid result has been obtained by the 5-FU measurement, the 5-FU dose in the subsequent cycle will be adapted only according to toxicity. 7) To make better use of the collected patient data and specimens, an additional purpose of use by the university of Bonn was specified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27256667