Clinical trial results:
Flucloxacillin as an inducer of CYP-enzymes

Summary

EudraCT number	2020-004044-28
Trial protocol	DK
Global end of trial date	28 December 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	Annotation for missing values (Annotation for missing values on secondary endpoint.pdf)

Trial information

Trial identification

Sponsor protocol code	AKF-396

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04840641
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Southern Denmark
Sponsor organisation address	J.B.Winsløws Vej 19, Odense, Denmark, 5000
Public contact	Clinical Pharmacology and Pharmacy, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark , dbiversen@health.sdu.dk
Scientific contact	Clinical Pharmacology and Pharmacy, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark , dbiversen@health.sdu.dk

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	11 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2021
Global end of trial reached?	Yes
Global end of trial date	28 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate if treatment with flucloxacillin increases drug metabolism in healthy volunteers through induction of cytochrome P450 (CYP) enzymes, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.
This study was a randomized, self-controlled cross-over study. 12 healthy volunteers completed the study according to the protocol.
Due to technical difficulties we were not able to calculate the changes of CYP2C19

Protection of trial subjects:

We measured blood pressure for the trial subjects to monitor the health of trial subjects after intake of the Basel Cocktail. Trial subjects were asked about adverse events during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2021
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	Denmark: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	14

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited healthy men and women from March 2021 until June 2021. All trial subjects consented to participate in the trial. If in- and exclusion criteria were fulfilled trial subjects were randomized to start in phase A or phase B. Based on In- and exclusion criteria a medical doctor decided if trial subjects could participate in the trial

Pre-assignment

Screening details:

Trial subjects were screened based on in and exclusion criteria. A medical doctor decided if trial subjects full-filled the criteria and could enter the trial.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

We measured the baseline level of CYP enzymes without intake of flucloxacillin.

All trial subjects worked as their own control and entered all periods. 5 people started in the Baseline period before entering the treatment period, and 7 people started in the treatment period before entering the Baseline period.

Arm type	No administration of drugs
Investigational medicinal product name	No drugs
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

No drugs were administered as the baseline level of CYP enzymes were measured in this arm

Number of subjects in period 1[1]	Baseline
Started	12
Completed	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: We included 14 healthy subjects. 2 subjects withdrew from the study, one due to adverse events and one due to personal reasons. We only based the analysis on 12 subjects as they all completed the study according to the protocol.

Period 2

Period 2 title	Flucloxacillin
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Flucloxacillin treatement

Arm description:

Trial subjects ingested flucloxacillin for 31 days. We measured induction of CYP-enzymes at 10 days and 28 days.

All trial subjects worked as their own control and entered all periods. 5 people started in the Baseline period before entering the treatment period, and 7 people started in the treatment period before entering the Baseline period.

Arm type	Experimental
Investigational medicinal product name	Flucloxacillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the trial, trial subjects ingested 1 gram flucloxacillin 3 times daily.

Number of subjects in period 2	Flucloxacillin treatement
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	23		
inter-quartile range (Q1-Q3)	22 to 24	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	8	8	

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

We measured the baseline level of CYP enzymes without intake of flucloxacillin.

All trial subjects worked as their own control and entered all periods. 5 people started in the Baseline period before entering the treatment period, and 7 people started in the treatment period before entering the Baseline period.

Reporting group title	Flucloxacillin treatement

Reporting group description:

Trial subjects ingested flucloxacillin for 31 days. We measured induction of CYP-enzymes at 10 days and 28 days.

All trial subjects worked as their own control and entered all periods. 5 people started in the Baseline period before entering the treatment period, and 7 people started in the treatment period before entering the Baseline period.

Primary: change in AUC of midazolam after 28 days of treatment

End point title	change in AUC of midazolam after 28 days of treatment

End point description:

Midazolam AUC after 28 days of flucloxacillin treatment

End point type	Primary

End point timeframe:

At baseline and 28 days of flucloxacillin treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[1]	12[2]		
Units: ng h ml^-1				
geometric mean (confidence interval 95%)				
Midazolam	0.7 (0.53 to 0.92)	0.73 (0.61 to 0.88)		

Notes:

[1] - Reporting group 1 is the change in AUC between baseline and 10 days of flucloxacillin

[2] - Reporting group 2 is the change in AUC between baseline and 28 days of flucloxacillin

Statistical analyses

Statistical analysis title	Geometric mean ratio

Statistical analysis description:

We only included trial subjects who finished the whole study according to the protocol. Based on this we excluded 2 trial subjects

Comparison groups	Flucloxacillin treatement v Baseline

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [3]
Method	No p-value
Parameter estimate	Geometric mean ratio

Notes:

[3] - We did not calculate p-values, but instead, the confidence interval 95%. If the geometric mean ration contained 1, it was not considered statistically significant.

Secondary: Change in AUC of the six substrates midazolam (substrate of CYP3A4), caffeine (CYP1A2), efavirenz (CYP2B6), losartan (CYP2C9), omeprazole (CYP2C19) and metoprolol (CYP2D6) and their main metabolites after 10 and 28 days

End point title	Change in AUC of the six substrates midazolam (substrate of CYP3A4), caffeine (CYP1A2), efavirenz (CYP2B6), losartan (CYP2C9), omeprazole (CYP2C19) and metoprolol (CYP2D6) and their main metabolites after 10 and 28 days

End point description:

End point type	Secondary

End point timeframe:

Comparing 10 and 28 days of flucloxacillin treatment with baseline measurements

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: ng*h ml^-1				
median (inter-quartile range (Q1-Q3))				
Caffeine	0.79 (0.74 to 0.84)	0.75 (0.63 to 0.89)		
Efairenz	1.0 (0.91 to 1.1)	1.18 (1.1 to 1.3)		
Losartan	0.9 (0.76 to 1.1)	0.82 (0.67 to 1.0)		
Metoprolol	0.8 (0.47 to 1.4)	0.62 (0.41 to 0.93)		
Midazolam	0.7 (0.53 to 0.92)	0.73 (0.61 to 0.88)		
1-OH-midazolam	0.85 (0.71 to 1.0)	0.89 (0.75 to 1.0)		
E3174	0.89 (0.84 to 0.93)	0.81 (0.71 to 0.92)		
OH-metoprolol	0.87 (0.45 to 1.7)	0.64 (0.19 to 2.1)		
Paraxanthine	0.81 (0.73 to 0.9)	0.78 (0.69 to 0.88)		
8-OH-efavirenz	0.69 (0.59 to 0.8)	0.84 (0.74 to 0.95)		
Omeprazole	0.87 (0.67 to 1.1)	0.82 (0.57 to 1.1)		
5-OH-omeprazole	0.84 (0.72 to 0.97)	0.78 (0.67 to 0.91)		

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [4]
Method	No p-value

Notes:

[4] - We did not calculate the p-value. Instead, we calculated the 95 % CI. if CI 95% for GMR contained 1, it was not considered statistically signifikant.

Secondary: Change in Cmax of the Basel Cocktail and their main metabolites

End point title	Change in Cmax of the Basel Cocktail and their main metabolites

End point description:

End point type	Secondary

End point timeframe:

Comparing data from baseline until day 10 and 28 of flucloxacillin treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: ng*ml^-1				
geometric mean (confidence interval 95%)				
Midazolam	0.92 (0.68 to 1.2)	1.0 (0.84 to 1.2)		
Losartan	0.98 (0.74 to 1.3)	0.88 (0.61 to 1.3)		
Metoprolol	0.8 (0.47 to 1.4)	0.7 (0.56 to 0.86)		
Caffeine	0.91 (0.84 to 0.99)	0.97 (0.89 to 1.1)		
Efavirenz	1.1 (0.94 to 1.3)	1.35 (1.1 to 1.7)		
1-OH-midazolam	1.0 (0.82 to 1.2)	1.1 (0.89 to 1.3)		
E3174	0.97 (0.85 to 1.1)	0.93 (0.8 to 1.1)		
OH-metoprolol	1.1 (0.77 to 1.7)	0.93 (0.55 to 1.6)		
Paraxanthine	1.0 (0.94 to 1.1)	1.0 (0.9 to 1.1)		

8-OH-efavirenz	0.78 (0.61 to 1.0)	0.82 (0.67 to 1.0)		
Omeprazole	0.91 (0.68 to 1.2)	0.8 (0.66 to 1.2)		
5-OH-omeprazole	0.9 (0.75 to 1.1)	0.86 (0.66 to 1.1)		

Statistical analyses

Statistical analysis title	Geometric mean ratio
Statistical analysis description:	
There were 12 subjects in this analysis as the study was self-controlled	
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [5]
Method	Not provided

Notes:

[5] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical signific

Secondary: Change in T1/2 of the Basel Cocktail and their main metabolites

End point title	Change in T1/2 of the Basel Cocktail and their main metabolites
End point description:	
End point type	Secondary
End point timeframe:	
Measuring baseline and comparing to 10 and 28 days of flucloxacillin treatment	

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: T1/2 (hours)				
geometric mean (confidence interval 95%)				
Midazolam	0.73 (0.6 to 0.9)	0.58 (0.43 to 0.79)		
losartan	1.0 (0.86 to 1.2)	0.9 (0.79 to 1.0)		
metoprolol	0.98 (0.64 to 1.5)	1.2 (0.56 to 2.4)		
caffeine	0.82 (0.8 to 0.85)	0.79 (0.7 to 0.9)		
efavirenz	1.01 (0.59 to 1.7)	1.2 (0.95 to 1.4)		
1-OH-midazolam	0.63 (0.28 to 1.4)	0.54 (0.24 to 1.2)		

E3174	0.99 (0.75 to 1.3)	0.83 (0.68 to 1.0)		
OH-metoprolol	1.3 (0.09 to 18.0)	0.97 (0.05 to 17.2)		
paraxanthine	0.87 (0.77 to 0.97)	0.83 (0.73 to 0.93)		
8-OH-efavirenz	1.0 (0.73 to 1.4)	1.1 (0.81 to 1.6)		
Omeprazole	1 (0.88 to 1.2)	0.85 (0.69 to 1.1)		
5-OH-omeprazole	0.89 (0.77 to 1)	0.84 (0.67 to 1.1)		

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [6]
Method	No p-value
Parameter estimate	GMR

Notes:

[6] - We did not calculate the p-value. Instead, we calculated the 95 % CI. if CI 95% for GMR contained 1, it was not considered statistically signifikant.

Secondary: change in AUCratio of the Basel Cocktail and their main metabolites

End point title	change in AUCratio of the Basel Cocktail and their main metabolites

End point description:

End point type	Secondary

End point timeframe:

Baseline measurements compared to 10 and 28 days of flucloxacillin treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: ratio				
geometric mean (confidence interval 95%)				
midazolam	1.2 (0.93 to 1.5)	1.3 (1.0 to 1.5)		
losartan	0.98 (0.83 to 1.2)	0.98 (0.82 to 1.2)		
metoprolol	1.0 (0.52 to 2.0)	0.90 (0.25 to 3.3)		
caffeine	1.0 (0.96 to 1.1)	1.0 (0.93 to 1.2)		

efavirenz	0.69 (0.57 to 0.83)	0.71 (0.63 to 0.80)		
Omeprazole	0.97 (0.8 to 1.2)	0.95 (0.7 to 1.3)		

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [7]
Method	No p-value

Notes:

[7] - We did not calculate the p-value. Instead, we calculated the 95 % CI. if CI 95% for GMR contained 1, it was not considered statistically signifikant.

Secondary: change in metabolic ratio of the Basel Cocktail and their main metabolites

End point title	change in metabolic ratio of the Basel Cocktail and their main metabolites

End point description:

End point type	Secondary

End point timeframe:

Baseline measurements compared to 10 and 28 days of flucloxacillin treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: ratio				
geometric mean (confidence interval 95%)				
midazolam	1.3 (1.1 to 1.6)	1.4 (1.2 to 1.6)		
losartan	1.1 (0.92 to 1.4)	1.1 (0.78 to 1.7)		
metoprolol	0.91 (0.57 to 1.5)	0.96 (0.4 to 2.3)		
caffeine	1.1 (1.1 to 1.2)	1.3 (1.0 to 1.6)		
efavirenz	0.65 (0.51 to 0.84)	0.61 (0.51 to 0.73)		
Omeprazole	0.98 (0.58 to 1.7)	1.14 (0.63 to 2.1)		

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [8]
Method	No p-value
Parameter estimate	Geometric mean ratio
Confidence interval	
level	95 %
sides	2-sided

Notes:

[8] - We calculated the 95% confidence interval instead of p-values.

Secondary: change in formation clearance of the Basel Cocktail and their main metabolites

End point title	change in formation clearance of the Basel Cocktail and their main metabolites

End point description:

End point type	Secondary

End point timeframe:

At baseline and after 10 and 28 days of flucloxacillin treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[9]	12[10]		
Units: ml*h^-1*1000				
geometric mean (confidence interval 95%)				
Midazolam	1.2 (0.76 to 1.8)	1.7 (1.1 to 2.6)		
Losartan	0.93 (0.71 to 1.2)	0.91 (0.6 to 1.4)		
Metoprolol	1.4 (0.87 to 2.1)	2.0 (1.3 to 2.9)		
Caffeine	1.4 (1.0 to 1.9)	1.3 (1 to 1.6)		
Efavirenz	0.78 (0.63 to 0.96)	0.77 (0.64 to 0.93)		

Notes:

[9] - Reporting group 1 is the change in AUC between baseline and 10 days of flucloxacillin

[10] - Reporting group 2 is the change in AUC between baseline and 28 days of flucloxacillin

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Flucloxacillin treatement v Baseline

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [11]
Method	No p-value was calculated
Parameter estimate	GMR

Notes:

[11] - We did not calculate the p-value. Instead, we calculated the 95 % CI. if CI 95% for GMR contained 1, it was not considered statistically signifikant.

Secondary: change in renal clearance of the Basel Cocktail and their main metabolites

End point title	change in renal clearance of the Basel Cocktail and their main metabolites

End point description:

End point type	Secondary

End point timeframe:

Baseline compared to 10 and 28 days of treatment

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[12]	12[13]		
Units: ml*h^-1*1000				
geometric mean (confidence interval 95%)				
Midazolam	0.89 (0.53 to 1.5)	1.5 (0.83 to 2.6)		
Losartan	0.78 (0.49 to 1.3)	0.76 (0.45 to 1.3)		
Metoprolol	0.88 (0.6 to 1.3)	1.2 (0.87 to 1.5)		
Caffeine	1.1 (0.61 to 1.7)	1.2 (0.66 to 2.2)		
Efavirenz	1 (0.75 to 1.5)	0.88 (0.6 to 1.3)		

Notes:

[12] - Reporting group 2 is the change in AUC between baseline and 28 days of flucloxacillin

[13] - Reporting group 2 is the change in AUC between baseline and 28 days of flucloxacillin

Statistical analyses

Statistical analysis title	Geometric mean ratio
Comparison groups	Baseline v Flucloxacillin treatement
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [14]
Method	No p-value was calculated
Parameter estimate	GMR

Notes:

[14] - We did not calculate the p-value. Instead, we calculated the 95 % CI. if CI 95% for GMR contained 1, it was not considered statistically signifikant.

Secondary: Change in Ae (amount in urine) of the Basel Cocktail and their main metabolite

End point title	Change in Ae (amount in urine) of the Basel Cocktail and their main metabolite

End point description:

End point type	Secondary

End point timeframe:

After 10 and 28 days of flucloxacillin treatment compared to baseline. Values are geometric mean values.

End point values	Baseline	Flucloxacillin treatement		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: mg				
geometric mean (confidence interval 95%)				
Midazolam	0.63 (0.41 to 0.97)	1.1 (0.55 to 2.03)		
Losartan	0.7 (0.45 to 1.1)	0.62 (0.37 to 1.1)		
Metorprolol	0.77 (0.57 to 1)	0.7 (0.54 to 0.94)		
Caffeine	0.89 (0.61 to 1.3)	0.95 (0.52 to 1.7)		
Efavirenz	1 (0.74 to 1.5)	1 (0.73 to 1.5)		
1-OH-midazolam	0.82 (0.68 to 1)	0.82 (0.59 to 1.1)		
E3174	0.83 (0.72 to 0.96)	0.62 (0.56 to 0.99)		
OH-metoprolol	1.2 (0.87 to 1.7)	1.2 (0.89 to 1.7)		
Paraxanthine	1.1 (0.8 to 1.5)	1 (0.84 to 1.2)		
8-OH-efavirenz	0.78 (0.66 to 0.91)	0.91 (0.75 to 1.1)		

Statistical analyses

Statistical analysis title	Geometric mean ratio

Statistical analysis description:

There were 12 subjects in this analysis as the study was self-controlled

Comparison groups	Baseline v Flucloxacillin treatement

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≥ 0.05 [15]
Method	No p-value
Parameter estimate	GMR

Notes:

[15] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical significant

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were were reported from intake of medicine in the trial and 2 weeks after the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	None
Dictionary version	0

Reporting groups	
Reporting group title	Ingesting flucloxacillin
Reporting group description:	
Adverse events for trial subjects ingesting flucloxacillin for 31 days	

Serious adverse events	Ingesting flucloxacillin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Ingesting flucloxacillin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 14 (78.57%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	6		

Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) heartburn subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5 1 / 14 (7.14%) 1 1 / 14 (7.14%) 1		
Infections and infestations Vaginal yeast infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported