

**Clinical trial results:****A Phase 1, Single-dose Study to Evaluate the Relative Bioavailability of Cobicistat (COBI) Age-Appropriate Pediatric Tablet Formulations Compared with Adult COBI****150-mg Tablets in Healthy Adult Volunteers****Summary**

EudraCT number	2015-000466-57
Trial protocol	Outside EU/EEA
Global end of trial date	05 January 2013

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	22 July 2015

Trial information**Trial identification**

Sponsor protocol code	GS-US-216-0127
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 101283

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000969-PIP01-10
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	05 January 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was to evaluate the relative bioavailability of 2 age-appropriate pediatric formulations (immediate release tablet or dispersible tablet as suspension) of cobicistat (COBI) in healthy adult participants.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 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	United States: 62
Worldwide total number of subjects	62
EEA total number of subjects	0

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)	62
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a single study site in the United States. The first participant was screened on 13 November 2012. The last study visit occurred on 05 January 2013.

Pre-assignment

Screening details:

120 participants were screened.

Period 1

Period 1 title	Overall 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	Cohort 1

Arm description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B)

Arm type	Experimental
Investigational medicinal product name	Cobicistat
Investigational medicinal product code	
Other name	Tybost®, GS-9350
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

COBI 150 mg adult immediate release tablet, 50 mg age-appropriate pediatric immediate release tablet, or 20 mg age-appropriate pediatric dispersible tablet as suspension formulation administered orally in the morning immediately after a standard meal

Arm title	Cohort 2
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Arm description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C)

Arm type	Experimental
Investigational medicinal product name	Cobicistat
Investigational medicinal product code	
Other name	Tybost®, GS-9350
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

COBI 150 mg adult immediate release tablet, 50 mg age-appropriate pediatric immediate release tablet, or 20 mg age-appropriate pediatric dispersible tablet as suspension formulation administered orally in the morning immediately after a standard meal

Number of subjects in period 1	Cohort 1	Cohort 2
Started	32	30
Completed	30	29
Not completed	2	1
Subject withdrew consent	1	-
Protocol violation	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B)

Reporting group title	Cohort 2
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Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C)

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	32	30	62
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	28 ± 6.9	29 ± 7.3	-
Gender categorical Units: Subjects			
Female	13	8	21
Male	19	22	41
Race Units: Subjects			
Asian	0	2	2
Black or African American	23	14	37
White	9	14	23
Ethnicity Units: Subjects			
Hispanic or Latino	2	5	7
Not Hispanic or Latino	30	25	55

End points

End points reporting groups

Reporting group title	Cohort 1
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Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 3 x 50 mg age-appropriate pediatric immediate release tablet (Treatment B)

Reporting group title	Cohort 2
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Reporting group description:

COBI 1 x 150 mg adult immediate release tablet (Treatment A) or COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet (Treatment C)

Subject analysis set title	Cohort 1, Treatment A
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 1 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) on Day 1 or 8

Subject analysis set title	Cohort 1, Treatment B
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) on Day 1 or 8

Subject analysis set title	Cohort 2, Treatment A
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) on Day 1 or 8

Subject analysis set title	Cohort 2, Treatment C
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) on Day 1 or 8

Subject analysis set title	Treatment A
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohorts 1 and 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) were analyzed.

Subject analysis set title	Treatment B
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) were analyzed.

Subject analysis set title	Treatment C
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) were analyzed.

Primary: Plasma Pharmacokinetics of COBI as measured by AUClast and AUCinf

End point title	Plasma Pharmacokinetics of COBI as measured by AUClast and AUCinf
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End point description:

AUClast is defined as the concentration of drug from time zero to the last quantifiable concentration.

AUCinf is defined as the concentration of drug extrapolated to infinite time.

Participants in the COBI PK Analysis Set were analyzed.

End point type	Primary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

End point values	Cohort 1, Treatment A	Cohort 1, Treatment B	Cohort 2, Treatment A	Cohort 2, Treatment C
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: ng*h/mL				
geometric mean (confidence interval 95%)				
AUClast	4705.1 (3906.5 to 5667)	4468.6 (3776.3 to 5287.7)	5664.3 (4720.7 to 6796.4)	5471.5 (4490.7 to 6666.7)
AUCinf	4748.7 (3942.6 to 5719.6)	4509.4 (3813.2 to 5332.6)	5707.4 (4761.3 to 6841.6)	5513.6 (4529.6 to 6711.4)

Statistical analyses

Statistical analysis title	Cohort 1: Treatment B/Treatment A for AUClast
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Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.

Comparison groups	Cohort 1, Treatment B v Cohort 1, Treatment A
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Number of subjects included in analysis	60
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Analysis specification	Pre-specified
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Analysis type	other ^[1]
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Parameter estimate	Geometric least-squares mean ratio
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Point estimate	94.97
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Confidence interval

level	90 %
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sides	2-sided
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lower limit	88.94
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upper limit	101.42
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Notes:

[1] - Intergroup comparison

Statistical analysis title	Cohort 1: Treatment B/Treatment A for AUCinf
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Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.

Comparison groups	Cohort 1, Treatment B v Cohort 1, Treatment A
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[2]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	94.96
Confidence interval	
level	90 %
sides	2-sided
lower limit	88.93
upper limit	101.39

Notes:

[2] - Intergroup comparison

Statistical analysis title	Cohort 2: Treatment C/Treatment A for AUClast
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Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

Comparison groups	Cohort 2, Treatment A v Cohort 2, Treatment C
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	96.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.01
upper limit	103.67

Notes:

[3] - Intergroup comparison

Statistical analysis title	Cohort 2: Treatment C/Treatment A for AUCinf
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Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

Comparison groups	Cohort 2, Treatment A v Cohort 2, Treatment C
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Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[4]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	96.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	90.07
upper limit	103.62

Notes:

[4] - Intergroup comparison

Primary: Plasma Pharmacokinetics of COBI as measured by Cmax

End point title	Plasma Pharmacokinetics of COBI as measured by Cmax
End point description:	
Cmax is defined as the maximum observed concentration of drug in plasma. Participants in the COBI PK Analysis Set were analyzed.	
End point type	Primary
End point timeframe:	
Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8	

End point values	Cohort 1, Treatment A	Cohort 1, Treatment B	Cohort 2, Treatment A	Cohort 2, Treatment C
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: ng/mL				
geometric mean (confidence interval 95%)	803.7 (707.5 to 913)	804.1 (699.9 to 923.8)	924.2 (800.6 to 1066.8)	849.5 (725.5 to 994.7)

Statistical analyses

Statistical analysis title	Cohort 1: Treatment B/Treatment A for Cmax
Statistical analysis description:	
A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 1: Treatment B/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment B.	
Comparison groups	Cohort 1, Treatment B v Cohort 1, Treatment A
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[5]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	100.05

Confidence interval	
level	90 %
sides	2-sided
lower limit	92.8
upper limit	107.86

Notes:

[5] - Intergroup comparison

Statistical analysis title	Cohort 2: Treatment C/Treatment A for Cmax
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Statistical analysis description:

A parametric mixed effect analysis of variance (ANOVA) model was used to estimate the geometric mean ratio (Cohort 2: Treatment C/Treatment A) of the PK parameter and the corresponding 90% CI. "Subjects in this analysis" states 60; however, only 30 unique participants were analyzed, each reported for Treatment A and Treatment C.

Comparison groups	Cohort 2, Treatment A v Cohort 2, Treatment C
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other ^[6]
Parameter estimate	Geometric least-squares mean ratio
Point estimate	91.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	86.77
upper limit	97.37

Notes:

[6] - Intergroup comparison

Secondary: Plasma Pharmacokinetics of COBI as measured by %AUCexp

End point title	Plasma Pharmacokinetics of COBI as measured by %AUCexp
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End point description:

%AUCexp is defined as the percent area under the plasma concentration-time curve. Participants in the COBI PK Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Pre-dose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

End point values	Cohort 1, Treatment A	Cohort 1, Treatment B	Cohort 2, Treatment A	Cohort 2, Treatment C
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: percent				
arithmetic mean (standard deviation)	0.9 (± 0.51)	0.9 (± 0.38)	0.8 (± 0.37)	0.8 (± 0.39)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Pharmacokinetics of COBI as measured by Tmax and t1/2

End point title	Plasma Pharmacokinetics of COBI as measured by Tmax and t1/2
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End point description:

Tmax is defined as the time of Cmax. t1/2 is defined as the estimate of the terminal elimination half-life of the drug. Participants in the COBI PK Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose on Days 1 and 8

End point values	Cohort 1, Treatment A	Cohort 1, Treatment B	Cohort 2, Treatment A	Cohort 2, Treatment C
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	30	30	30
Units: hours				
median (inter-quartile range (Q1-Q3))				
Tmax	2.5 (2 to 3.05)	2.51 (2.5 to 3.02)	2.5 (2.5 to 3.5)	3.25 (2.5 to 4.5)
t1/2	3.27 (2.74 to 3.86)	3.16 (2.73 to 3.8)	3.36 (3 to 3.58)	3.2 (2.76 to 3.72)

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability for COBI formulations as measured by palatability rating

End point title	Acceptability for COBI formulations as measured by palatability rating
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End point description:

Palatability ratings were assessed using a scale of 1 (dislike very much) to 7 (like very much). Participants in the Safety Analysis Set were analyzed by treatment received.

End point type	Secondary
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End point timeframe:

Days 1 and 8

End point values	Treatment A	Treatment B	Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	62	31	30	
Units: units on a scale				
arithmetic mean (standard deviation)	5 (\pm 1.5)	6 (\pm 1.6)	4 (\pm 1.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 15 days plus 30 days

Adverse event reporting additional description:

Safety Analysis Set

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Treatment A
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Reporting group description:

Participants in Cohorts 1 and 2 who received Treatment A (COBI 1 x 150 mg adult immediate release tablet) were analyzed.

Reporting group title	Treatment B
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Reporting group description:

Participants in Cohort 1 who received Treatment B (COBI 3 x 50 mg age-appropriate pediatric immediate release tablet) were analyzed.

Reporting group title	Treatment C
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Reporting group description:

Participants in Cohort 2 who received Treatment C (COBI 7.5 x 20 mg age-appropriate pediatric dispersible tablet) were analyzed.

Serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 62 (0.00%)	0 / 31 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Treatment A	Treatment B	Treatment C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 62 (3.23%)	3 / 31 (9.68%)	1 / 30 (3.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 62 (3.23%)	3 / 31 (9.68%)	1 / 30 (3.33%)
occurrences (all)	2	3	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