Clinical trial results:
Efficacy and Safety of Inhaled Budesonide in Very Preterm Infants at Risk for Bronchopulmonary Dysplasia

Summary

EudraCT number	2009-012203-26
Trial protocol	DE FI FR EE CZ BE GR NL
Global end of trial date	31 July 2016

Results information

Result version number	v1 (current)
This version publication date	25 March 2022
First version publication date	25 March 2022
Summary attachment (see zip file)	Safety outcomes (Safety outcomes.jpeg)

Trial information

Trial identification

Sponsor protocol code	Grand_Award_Health-F5_2009-223060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01035190
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Children's Hospital Tuebingen
Sponsor organisation address	Calwerstr. 7, Tuebingen, Germany, 72976
Public contact	Christian F. Poets, Dirk Bassler, University Children's Hospital Tuebingen Department of Neonatology, +49 7071-298 6175/61, neurosis.studycoordinator@med.uni-tuebingen.de
Scientific contact	Christian F. Poets, Dirk Bassler, University Children's Hospital Tuebingen Department of Neonatology, +49 7071-298 6175/61, neurosis.studycoordinator@med.uni-tuebingen.de

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	15 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if the early (within 12 hours of life) prophylactic use of inhaled corticosteroids (Budesonide) in very preterm infants (gestational age 23 0/7-27 6/7 weeks) requiring any form of positive pressure support (mechanical or nasal ventilation or continuous positive airway pressure (CPAP)) increases survival without bronchopulmonary dysplasia (BPD) at 36 weeks gestational age.

Protection of trial subjects:

NEuroSIS will be conducted in accordance with the Declaration of Helsinki, as well as with the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP). At present there is general agreement that further studies investigating inhaled corticosteroids in the population of preterm infants are needed and equipoise remains. It has been highlighted repeatedly that future studies need to address both the short-term and longterm benefits and adverse effects, with particular attention to neurodevelopmental outcome.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 April 2010
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	Israel: 125
Country: Number of subjects enrolled	Germany: 252
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Czechia: 179
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 103
Country: Number of subjects enrolled	France: 100
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Belgium: 34
Worldwide total number of subjects	863
EEA total number of subjects	738

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	863
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 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronologic age of 12 hours or less who required any form of positivepressure support were eligible.

Pre-assignment

Screening details:

2233 infants met the inclusion criteria, however, 466 patients were excluded due to several reasons. 1767 patients were available, but only 913 underwent randomization. Finally the ITT population consisted of 863 patients

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Data relating to patients/parents, caregivers and outcome assessors will be blinded (the pharmacist will be the only person with knowledge of treatment assignments). Randomization must take place within the first 12 hours of life.

Arms

Are arms mutually exclusive?	Yes
Arm title	Budenoside arm

Arm description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

Arm type	Experimental
Investigational medicinal product name	Budesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oromucosal suspension
Routes of administration	Inhalation use

Dosage and administration details:

The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

Arm title	Placebo arm

Arm description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

The dose was two puffs administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered. Study drugs were administered until infants no longer needed supplemental oxygen and positivepressure support or reached a postmenstrual age of 32 weeks 0 days, regardless of ventilator status.

Number of subjects in period 1	Budenoside arm	Placebo arm
Started	441	422
Completed	437	419
Not completed	4	3
Consent withdrawn by subject	4	3

Baseline characteristics

Reporting groups

Reporting group title	Budenoside arm

Reporting group description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

Reporting group title	Placebo arm

Reporting group description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

Reporting group values	Budenoside arm	Placebo arm	Total
Number of subjects	441	422	863
Age categorical			
Infants with a gestational age of 23 weeks 0 days to 27 weeks 6 days and a chronologic age of 12 hours or less who required any form of positivepressure support were eligible.			
Units: Subjects			
Preterm newborn infants (gestational age < 37 wks)	1	1	2
Newborns (0-27 days)	439	420	859
Infants and toddlers (28 days-23 months)	1	1	2
Age continuous			
Units: weeks			
arithmetic mean	26.1	26.1	
standard deviation	± 1.3	± 1.2	-
Gender categorical			
Units: Subjects			
Female	219	209	428
Male	222	213	435

End points

End points reporting groups

Reporting group title	Budenoside arm

Reporting group description:

Eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The dose of budesonide was two puffs (200 µg per puff) administered every 12 hours in the first 14 days of life and one puff administered every 12 hours from day 15 until the last dose of the study drug had been administered.

Reporting group title	Placebo arm

Reporting group description:

To ensure that all the infants received the study drug within 24 hours after birth, eligible infants received the first dose within 12 hours after random assignment. Study drugs were administered by means of a metered-dose inhaler connected to a spacer. This spacer, which had a capacity of 110 ml, was filled with a sufficient amount of oxygen to keep the infant in the targeted oxygensaturation range. For infants receiving mechanical ventilation, the spacer was inserted into the ventilator circuit close to the endotracheal tube. For infants receiving nasal respiratory support, the spacer was connected to a face mask. The placebo contained only hydrofluoroalkane propellant.

Primary: Death or bronchopulmonary displasia at 36 weeks postmenstrual age

End point title	Death or bronchopulmonary displasia at 36 weeks postmenstrual age

End point description:

The primary outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. Bronchopulmonary dysplasia
was defined as the requirement for positivepressure support, the requirement for supplemental oxygen at a fraction of inspired oxygen exceeding 0.30, or, in infants receiving low amounts of oxygen, an inability to maintain an oxygen-saturation value above 90% during a structured, short period of saturation monitoring
coupled with gradual weaning from oxygen to ambient air (the oxygen-reduction test).

End point type	Primary

End point timeframe:

36 weeks

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	175	194		

Statistical analyses

Statistical analysis title	Statistical analysis of the primary endpoint
Comparison groups	Budenoside arm v Placebo arm

Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1

Secondary: Frequency of a patent ductus arteriosus requiring surgery

End point title	Frequency of a patent ductus arteriosus requiring surgery

End point description:

The frequency of a patent ductus arteriosus that was considered by clinical staff to require surgical ligation

End point type	Secondary

End point timeframe:

36 weeks

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	31	54		

Statistical analyses

Statistical analysis title	Statistical analysis secondary outcome
Comparison groups	Placebo arm v Budenoside arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.83

Secondary: Frequency of the need for reintubation after the last administration of thestudy drug

End point title	Frequency of the need for reintubation after the last administration of thestudy drug
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	23	38		

Statistical analyses

Statistical analysis title	Statistical analysis of the secondary outcome
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.03
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.96

Secondary: The median postmenstrual age at the last use of supplemental oxygen

End point title	The median postmenstrual age at the last use of supplemental oxygen
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: weeks	32	33		

Statistical analyses

Statistical analysis title	Statistical analysis of the secondary outcome
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	ANOVA

Secondary: Retinopathy of prematurity

End point title	Retinopathy of prematurity

End point description:

The endpoint was to assess how many participants developed stage 2 or higher retinopathy of prematurity

End point type	Secondary

End point timeframe:

36 weeks

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	363	361		
Units: patients	127	113		

Statistical analyses

Statistical analysis title	Stratified relative risk
Comparison groups	Budenoside arm v Placebo arm

Number of subjects included in analysis	724
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.23
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.38

Secondary: Brain injury

End point title	Brain injury
End point description:	
The endpoint was to assess how many patients suffered from brain injury	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	428	410		
Units: patients	91	70		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.12
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.65

Secondary: Necrotizing enterocolitis or intestinal perforation

End point title	Necrotizing enterocolitis or intestinal perforation
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	51	44		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.47
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.35

Secondary: Frecuency of intestinal perforation

End point title	Frecuency of intestinal perforation
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	29	44		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.95
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.58

Secondary: Patent ductus arteriosus treated with drugs

End point title	Patent ductus arteriosus treated with drugs
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	189	207		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Placebo arm v Budenoside arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.07
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.01

Secondary: Patent ductus arteriosus treated by surgical ligation

End point title	Patent ductus arteriosus treated by surgical ligation
End point description:	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	31	54		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.004
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.83

Secondary: Culture-proven infection: sepsis

End point title	Culture-proven infection: sepsis
End point description:	

End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	148	125		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.38

Secondary: Culture-proven infection: meningitis

End point title	Culture-proven infection: meningitis
End point description:	

End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	422		
Units: patients	5	4		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	859
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.79
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	4.43

Secondary: Adverse treatment effects

End point title	Adverse treatment effects
End point description:	
Adverse treatment effects were defined as either oral candidiasis requiring treatment (in 28 patients in the budesonide group and 32 patients in the placebo group), hyperglycemia requiring insulin treatment (in 86 patients in the budesonide group and 85 patients in the placebo group), or hypertension requiring treatment (in 6 patients in the budesonide group and 10 patients in the placebo group).	
End point type	Secondary
End point timeframe:	
36 weeks	

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	95	98		

Statistical analyses

Statistical analysis title	Stratified Relative Risk
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.55
Method	ANOVA
Parameter estimate	Risk ratio (RR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.18

Secondary: Days of hospitalization

End point title	Days of hospitalization

End point description:

End point type	Secondary

End point timeframe:

n.a

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: days	91	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in weight from baseline to day 28

End point title	Change in weight from baseline to day 28

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	422		
Units: grams (g)	274	278		

Statistical analyses

Statistical analysis title	p value for the change in weight
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	863
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.72
Method	ANOVA

Secondary: Change in head circumference from baselineto day 28

End point title	Change in head circumference from baselineto day 28

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: cm				
arithmetic mean (standard deviation)	1.6 (± 1.2)	1.4 (± 1.4)		

Statistical analyses

Statistical analysis title	P-value for the change in head circunference
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.21
Method	ANOVA

Secondary: Postmenstrual age at last use of respiratory support: Positive-pressure support

End point title	Postmenstrual age at last use of respiratory support: Positive-pressure support

End point description:

End point type	Secondary

End point timeframe:

n.a

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: weeks				
median (inter-quartile range (Q1-Q3))	33.1 (30.7 to 35.4)	33.4 (31.4 to 36.3)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.07
Method	ANOVA

Secondary: Postmenstrual age at last use of respiratory support: supplemental oxygen

End point title	Postmenstrual age at last use of respiratory support: supplemental oxygen

End point description:

End point type	Secondary

End point timeframe:

n.a

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: weeks				
median (inter-quartile range (Q1-Q3))	31.6 (27.9 to 35.4)	33.1 (28.3 to 37.1)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	Budenoside arm v Placebo arm
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	ANOVA

Secondary: Long term neurodevelopmental disability

End point title	Long term neurodevelopmental disability

End point description:

The only prespecified secondary long-term outcome was neurodevelopmental disability among survivors, defined as a composite of cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18 to 22 months.

End point type	Secondary

End point timeframe:

18 to 22 months

End point values	Budenoside arm	Placebo arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	419		
Units: patients	148	165		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: The long term effects were measured at 18 to 22 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	n.a
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The information regarding safety outcomes can be found in the attached chart.

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26465983