Clinical trial results:
Treatment of Optic Neuritis with Erythropoietin: a randomised, double-blind, placebo-controlled trial

Summary

EudraCT number	2013-002515-10
Trial protocol	DE
Global end of trial date	26 November 2019

Results information

Result version number	v1 (current)
This version publication date	16 December 2020
First version publication date	16 December 2020

Trial information

Trial identification

Sponsor protocol code	P000053

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01962571
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00005298

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
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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	26 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2019
Global end of trial reached?	Yes
Global end of trial date	26 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determination of the efficacy of erythropoietin compared to placebo given as add-on to methylprednisolone (standard of care) as assessed by measurements of global retinal nerve fibre layer thickness (RNFLT-G) and low contrast visual acuity (LCVA) 6 months after randomisation

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) was established. The DMC consisted of two physicians and one statistician. The function of the DMC was to monitor the course of the study and if necessary to give a recommendation to the steering committee for discontinuation, modification or continuation of the study. The underlying principles for the DMC were ethical and safety aspects for the patients. It was the task of the DMC to examine whether the conduct of the study was still ethically justifiable, whether security of the patients was ensured, and whether the process of the study is acceptable. For this purpose, the DMC had to be informed about the adherence to the protocol, the patient recruitment, the observed serious adverse events, and deaths. Serious adverse events were reported to the DMC at regular intervals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
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	Germany: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	103
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

108 patients were enrolled and randomized. 53 patients were randomized to placebo and 55 to EPO. In the EPO group, one patient was a screen failure. In each group one patient was lost to follow-up with no post baseline OCT reading. In the placebo group, one patient withdrew informed consent and one violated diagnosis inclusion criterion.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Epoetin alfa

Arm description:

Eopeotin alfa HEXAL (R) 40,000 IU/1 ml solution for injection in a pre-filled syringe

Arm type	Experimental
Investigational medicinal product name	Epoetin alfa
Investigational medicinal product code	
Other name	Epoetin alfa HEXAL® 40,000 IU/1 ml solution for injection in a pre-filled syringe
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 33,000 IU (approx. 0.85 ml) administered on days 1, 2 and 3 immediately after methylprednisolone.

Arm title	Sodium chloride

Arm description:

0.85 ml isotone sodium chloride solution (0.9%) solution for injection, 1x daily, 3 consecutive days

Arm type	Placebo
Investigational medicinal product name	Sodium choride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.9% saline solution i.v., 1x daily, 3 consecutive days. Dose: 0.85 ml

Number of subjects in period 1	Epoetin alfa	Sodium chloride
Started	52	51
Completed	52	51

Baseline characteristics

Reporting groups	
Reporting group title	Epoetin alfa
Reporting group description:	
Eopeotin alfa HEXAL (R) 40,000 IU/1 ml solution for injection in a pre-filled syringe	
Reporting group title	Sodium chloride
Reporting group description:	
0.85 ml isotone sodium chloride solution (0.9%) solution for injection, 1x daily, 3 consecutive days	

Reporting group values	Epoetin alfa	Sodium chloride	Total
Number of subjects	52	51	103
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	52	51	103
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	38	33	71
Male	14	18	32

End points

End points reporting groups	
Reporting group title	Epoetin alfa
Reporting group description:	
Eopeotin alfa HEXAL (R) 40,000 IU/1 ml solution for injection in a pre-filled syringe	
Reporting group title	Sodium chloride
Reporting group description:	
0.85 ml isotone sodium chloride solution (0.9%) solution for injection, 1x daily, 3 consecutive days	

Primary: Retinal fiber layer thickness (RNFLT-G-12) 3.5	
End point title	Retinal fiber layer thickness (RNFLT-G-12) 3.5
End point description:	
Global RNFL Thickness 3.5 [µm] fellow eye at baseline minus affected eye at Week 26 - Population FAS	
End point type	Primary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	46		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	15.93 (± 14.91)	14.65 (± 15.60)		

Statistical analyses

Statistical analysis title	Adjusted difference
Comparison groups	Sodium chloride v Epoetin alfa
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted difference
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.51
upper limit	7.55

Primary: Low contrast visual acuity (LCVA)	
End point title	Low contrast visual acuity (LCVA)
End point description:	
Low contrast visual acuity (2.5% Sloan chart score) at Week 26 - study eye - Population FAS	
End point type	Primary
End point timeframe:	
26 weeks after randomization	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	49		
Units: Sloan chart score				
arithmetic mean (standard deviation)	49.60 (± 21.31)	49.06 (± 21.93)		

Statistical analyses

Statistical analysis title	Adjusted difference
Comparison groups	Epoetin alfa v Sodium chloride
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted difference
Point estimate	-4.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.06
upper limit	5.01

Secondary: RNFLT-PMB-12	
End point title	RNFLT-PMB-12
End point description:	
PMB RNFL Thickness 3.5 [µm] fellow eye at baseline minus affected eye at Week 26 - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	45		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	12.38 (± 12.51)	11.96 (± 12.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: RNFLT temporal (RNFLT-T-12)

End point title	RNFLT temporal (RNFLT-T-12)

End point description:

Temporal RNFL Thickness 3.5 [µm] fellow eye at baseline minus affected eye at Week 26 - Population FAS

End point type	Secondary

End point timeframe:

Week 26

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	46		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	17.64 (± 16.89)	17.98 (± 14.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total macular volume (TMV)

End point title	Total macular volume (TMV)

End point description:

RNFL volume (ETDRS) [mm^3] fellow eye at baseline minus affected eye at Week 26 - Population FAS

End point type	Secondary

End point timeframe:

Week 26

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	42		
Units: cubic millimeters				
arithmetic mean (standard deviation)	0.19 (± 0.13)	0.14 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global RNFL Thickness 3.5 [µm]

End point title	Global RNFL Thickness 3.5 [µm]
End point description:	
Global RNFL Thickness 3.5 [µm] - study eye - Population FAS	
End point type	Secondary
End point timeframe:	
26 weeks	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	85.7 (± 18.1)	84.7 (± 18.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Temporal RNFL Thickness 3.5 [µm]

End point title	Temporal RNFL Thickness 3.5 [µm]
End point description:	
Temporal RNFL Thickness 3.5 [µm] - study eye - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	52.4 (± 16.6)	53.8 (± 18.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Temporal superior RNFL Thickness 3.5 [µm]

End point title	Temporal superior RNFL Thickness 3.5 [µm]
End point description:	
Temporal superior RNFL Thickness 3.5 [µm] - study eye - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	113.4 (± 31.0)	113.9 (± 34.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PMB RNFL Thickness 3.5 [µm]

End point title	PMB RNFL Thickness 3.5 [µm]
End point description:	
PMB RNFL Thickness 3.5 [µm] - study eye - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	46		
Units: micrometer (µm)				
arithmetic mean (standard deviation)	39.7 (± 11.8)	40.2 (± 12.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total macular volume (TMV)

End point title	Total macular volume (TMV)

End point description:

Total macular volume (TMV) [mm³] - study eye - at week 26 - Population FAS

End point type	Secondary

End point timeframe:

Week 26

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: cubic millimeters				
arithmetic mean (standard deviation)	8.43 (± 0.43)	7.99 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life

End point title	Quality of life

End point description:

NEI VQF25 summary score at Week 26

End point type	Secondary

End point timeframe:

Week 26

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	46		
Units: NEI VQF25 summary score				
arithmetic mean (standard deviation)	90.7 (± 11.8)	89.0 (± 11.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life - change from baseline

End point title	Quality of life - change from baseline
End point description: NEI VQF25 summary score - change from baseline to Week 26	
End point type	Secondary
End point timeframe: change from baseline to Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	45		
Units: NEI VQF25 summary score				
arithmetic mean (standard error)	16.4 (± 14.6)	23.7 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: EDSS

End point title	EDSS
End point description: Expanded Disability Status Scale (EDSS) score	
End point type	Secondary
End point timeframe: Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	47		
Units: EDSS score				
arithmetic mean (standard deviation)	0.37 (± 0.77)	0.72 (± 0.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: VEP latency - fellow eye

End point title	VEP latency - fellow eye
End point description:	
VEP latency at Week 26: Fellow eye - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: msec				
arithmetic mean (standard deviation)	105.38 (± 12.88)	106.06 (± 12.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: VEP latency - study eye

End point title	VEP latency - study eye
End point description:	
VEP latency at Week 26: Study eye - Population FAS	
End point type	Secondary
End point timeframe:	
Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	48		
Units: msec				
arithmetic mean (standard deviation)	120.99 (± 20.42)	118.72 (± 20.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: VEP amplitude - fellow eye

End point title	VEP amplitude - fellow eye
End point description: VEP amplitude at Week 26: Fellow eye - Population FAS	
End point type	Secondary
End point timeframe: Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	46		
Units: µV				
arithmetic mean (standard deviation)	11.94 (± 5.64)	10.73 (± 5.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: VEP amplitude - study eye

End point title	VEP amplitude - study eye
End point description: VEP amplitude at Week 26: Study eye - Population FAS	
End point type	Secondary
End point timeframe: Week 26	

End point values	Epoetin alfa	Sodium chloride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	46		
Units: µV				
arithmetic mean (standard deviation)	9.52 (± 5.02)	8.84 (± 5.35)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Complete study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	Epoetin alfa
Reporting group description:	
Epoetin alfa: Eopeotin alfa HEXAL (R) 40,000 IU/1 ml solution for injection in a pre-filled syringe	
Reporting group title	Placebo
Reporting group description:	
Sodium chloride (Placebo): 0.85 ml isotone sodium chloride solution (0.9%) solution for injection, 1x daily, 3 consecutive days	

Serious adverse events	Epoetin alfa	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 53 (15.09%)	4 / 52 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasal sinus cancer			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			

subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Anal fistula excision			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transverse sinus thrombosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Epoetin alfa	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 53 (79.25%)	42 / 52 (80.77%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pleomorphic adenoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 53 (0.00%)	4 / 52 (7.69%)	
occurrences (all)	0	5	
Hypertension			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Peripheral coldness			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Removal of foreign body from eye			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Tonsillectomy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Tumour excision			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site erosion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed	7 / 53 (13.21%)	5 / 52 (9.62%)	
occurrences (all)	7	5	
General physical health deterioration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hunger			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	2 / 53 (3.77%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Malaise			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Drug hypersensitivity			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Rhinitis allergic			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Panic attack			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	3 / 53 (5.66%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	3 / 53 (5.66%)	2 / 52 (3.85%)	
occurrences (all)	3	2	
Headache			
subjects affected / exposed	15 / 53 (28.30%)	13 / 52 (25.00%)	
occurrences (all)	26	17	
Hemianaesthesia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hypoaesthesia			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	
occurrences (all)	3	0	
Trigeminal neuralgia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Diplopia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	

Eye pain			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Keratitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Ocular discomfort			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	
occurrences (all)	2	2	
Visual impairment			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	3 / 53 (5.66%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Dyspepsia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Gastric disorder			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	6 / 53 (11.32%)	3 / 52 (5.77%)	
occurrences (all)	6	3	
Toothache			

subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Drug eruption			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Erythema			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	2 / 53 (3.77%)	2 / 52 (3.85%)	
occurrences (all)	2	2	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 53 (3.77%)	1 / 52 (1.92%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	5 / 53 (9.43%)	4 / 52 (7.69%)	
occurrences (all)	5	4	
Groin pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Neck pain			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Pain in extremity			
subjects affected / exposed	4 / 53 (7.55%)	0 / 52 (0.00%)	
occurrences (all)	4	0	
Spinal pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Cystitis			

subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Gastroenteritis viral			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Laryngitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Lyme disease			
subjects affected / exposed	1 / 53 (1.89%)	0 / 52 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	11 / 53 (20.75%)	9 / 52 (17.31%)	
occurrences (all)	15	12	
Otitis media			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	
occurrences (all)	0	2	
Respiratory tract infection			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	3 / 53 (5.66%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 52 (3.85%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 52 (1.92%)	
occurrences (all)	1	1	
Vitamin D deficiency			
subjects affected / exposed	2 / 53 (3.77%)	0 / 52 (0.00%)	
occurrences (all)	2	0	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26932144