Clinical trial results:
Anti-Influenza Hyperimmune Intravenous Immunoglobulin Clinical Outcome Study (INSIGHT 006: FLU-IVIG)

Summary

EudraCT number	2014-004271-22
Trial protocol	GB DK ES GR
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	INSIGHTPROTOCOL006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02287467
WHO universal trial number (UTN)	-
Other trial identifiers	ClinicalTrials.gov Identifier: NCT02287467

Notes:

Sponsors

Sponsor organisation name	Regents of the University of Minnesota
Sponsor organisation address	Office of the Vice President for Research, 420 Johnston Hall, 101 Pleasant St SE, Minneapolis, United States, 55455
Public contact	Chief Investigator- Sarah Pett, Medical Research Coucil Clinical Trials Unit at University College London, 44 02076704618, s.pett@ucl.ac.uk
Scientific contact	Chief Investigator- Sarah Pett, Medical Research Coucil Clinical Trials Unit at University College London, 44 02076704618, s.pett@ucl.ac.uk

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	07 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2018
Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the clinical status of patients in the IVIG and placebo groups at 7 days of follow-up using an ordinal outcome with 6 clinical states.
Specifically, patients will be categorized into one of the following 6 mutually exclusive categories on Day 7:
1) death;
2) Hospitalization in the intensive care unit (ICU);
3) non-ICU hospitalization, requiring supplemental oxygen;
4) non-ICU hospitalization, not requiring supplemental oxygen;
5) not hospitalized, but unable to resume normal activities; or
6) not hospitalized with resumption of normal activities.

The rationale behind this approach is to estimate in a clinically meaningful way whether the study drug has had a favourable clinical impact on the patient.

Protection of trial subjects:

Thics committee review and approval required at each study site. All participants (or their legally-authorized representatives) went through an informed consent process before any study procedures were done. Study product was infused over at least two hours to reduce potential side effects, and infusion could be paused or halted as needed in response to participant symptoms. Serious adverse reactions were reported and reviewed by the sponsor medical officer as they occurred. An independent DSMB reviewed unblinded study results approximately annually.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2015
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	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Thailand: 84
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	United States: 176
Country: Number of subjects enrolled	Mexico: 3

Worldwide total number of subjects	329
EEA total number of subjects	48

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)	228
From 65 to 84 years	85
85 years and over	16

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Individuals were considered to have been "screened" if they signed a consent for the study. However, only individuals who were ultimately randomized were considered to be study participants. One individual who signed consent was not randomized. It is not documented in the database why this individual was ultimately not randomized.

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, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	IVIG

Arm description:

anti-influenza immune globulin intravenous injection in normal saline to total 500 mL, given in a single infusion over approximately 2 hours.

Arm type	Experimental
Investigational medicinal product name	anti-influenza immune globulin (human) intravenous injections
Investigational medicinal product code	PDR5851619
Other name	anti-influenza IVIG
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

0.25 g/kg (to a maximum of 24.75 g) with normal saline to a total volume of 500 mL, in a single infusion over approximately 2 hours.

Arm title	Placebo

Arm description:

normal saline, 500 mL in a single infusion over approximately 2 hours

Arm type	Placebo
Investigational medicinal product name	normal saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Single dose of 500 mL to be delivered by intravenous infusion over approximately 2 hours.

Number of subjects in period 1	IVIG	Placebo
Started	168	161
Completed	156	152
Not completed	12	9
Consent withdrawn by subject	2	2
Protocol deviation	10	7

Baseline characteristics

Reporting groups	
Reporting group title	IVIG
Reporting group description:	
anti-influenza immune globulin intravenous injection in normal saline to total 500 mL, given in a single infusion over approximately 2 hours.	
Reporting group title	Placebo
Reporting group description:	
normal saline, 500 mL in a single infusion over approximately 2 hours	

Reporting group values	IVIG	Placebo	Total
Number of subjects	168	161	329
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	55.5	57.0	
inter-quartile range (Q1-Q3)	41.0 to 67.0	48.0 to 67.0	-
Gender categorical			
Units: Subjects			
Female	88	92	180
Male	80	69	149

End points

End points reporting groups

Reporting group title	IVIG
Reporting group description:	
anti-influenza immune globulin intravenous injection in normal saline to total 500 mL, given in a single infusion over approximately 2 hours.	
Reporting group title	Placebo
Reporting group description:	
normal saline, 500 mL in a single infusion over approximately 2 hours	

Primary: Day 7 status

End point title	Day 7 status
End point description:	
Mutually exclusive ordinal outcome: Death, in ICU, hospitalized on oxygen therapy, hospitalized not on oxygen therapy, discharged but not back to normal activities, back to normal activities	
End point type	Primary
End point timeframe:	
Day 7 after randomization (randomization=Day 0)	

End point values	IVIG	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152[1]	152[2]		
Units: participants				
Death	3	2		
In ICU	6	11		
Hospitalized, on oxygen	15	16		
Hospitalized, NOT on oxygen	8	12		
Discharged, not back to normal activities	56	51		
Back to normal activities	68	60		

Notes:

[1] - Completed trial, had outcome

[2] - Completed trial (did not withdraw consent, not excluded due to protocol violation)

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Comparison groups	IVIG v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	proportional hazards regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.97

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout trial (randomization through Day 28 visit)

Adverse event reporting additional description:

All Grade 3 and Grade 4 events were reported at study visits for all participants, and indicated whether the event was considered serious. No assessment of relatedness was made for non-serious events. Serious adverse events were reported as they occurred.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	IVIG

Reporting group description:

anti-influenza immune globulin intravenous injection in normal saline to total 500 mL, given in a single infusion over approximately 2 hours.

Reporting group title	Placebo

Reporting group description:

normal saline, 500 mL in a single infusion over approximately 2 hours

Serious adverse events	IVIG	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 166 (15.06%)	26 / 159 (16.35%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	6	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 166 (0.60%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 166 (1.20%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 166 (0.60%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Dysthymic disorder			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (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			
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 166 (1.20%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 166 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Internal hernia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 166 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	2 / 166 (1.20%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (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	IVIG	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 166 (17.47%)	30 / 159 (18.87%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Hypotension			
subjects affected / exposed	3 / 166 (1.81%)	1 / 159 (0.63%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal			

disorders			
Bronchial secretion retention			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Bronchospasm			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	5 / 166 (3.01%)	4 / 159 (2.52%)	
occurrences (all)	5	4	
Dyspnoea			
subjects affected / exposed	4 / 166 (2.41%)	3 / 159 (1.89%)	
occurrences (all)	4	4	
Lung consolidation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Respiratory acidosis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Confusional state			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Blood albumin decreased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 166 (0.60%)	2 / 159 (1.26%)	
occurrences (all)	2	2	
Blood calcium decreased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	3 / 166 (1.81%)	1 / 159 (0.63%)	
occurrences (all)	4	1	
Blood glucose increased			
subjects affected / exposed	1 / 166 (0.60%)	2 / 159 (1.26%)	
occurrences (all)	1	3	
Blood sodium increased			

subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Blood pressure increased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Coma scale abnormal			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	2 / 166 (1.20%)	4 / 159 (2.52%)	
occurrences (all)	4	6	
Lymphocyte count decreased			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 166 (0.60%)	3 / 159 (1.89%)	
occurrences (all)	2	4	
Platelet count increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Prothrombin time prolonged			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Arrhythmia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Myocardial ischaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 166 (1.20%)	1 / 159 (0.63%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 159 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 166 (0.60%)	3 / 159 (1.89%)	
occurrences (all)	1	3	
Dry mouth			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 166 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	4	

Vomiting			
subjects affected / exposed	0 / 166 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Autoimmune dermatitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Rash pruritic			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	0 / 166 (0.00%)	2 / 159 (1.26%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Muscle rigidity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 159 (0.63%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 166 (1.20%)	4 / 159 (2.52%)	
occurrences (all)	2	4	
Pain in extremity			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 159 (0.63%)	
occurrences (all)	1	1	
Hyperglycaemia			

subjects affected / exposed	1 / 166 (0.60%)	4 / 159 (2.52%)	
occurrences (all)	1	4	
Hyperkalaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 159 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2016	Protocol Version 2.0, Major changes: 1 eligibility criterion removed, 1 clarified. Primary endpoint definition clarified. Updates to align protocol with newest Investigator's Brochure. Other minor clarifications throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported