EU Clinical Trials Register

Clinical trial results:
What is the effect of intravenous iron supplementation on cardiopulmonary haemodynamics, exercise capacity and quality of life in patients with IPAH and iron deficiency?

Summary

EudraCT number	2010-024585-22
Trial protocol	GB DE
Global end of trial date	22 December 2017

Results information

Result version number	v1 (current)
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	WILK3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01447628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom,
Public contact	Luke Howard, Luke Howard, l.howard@imperial.ac.uk
Scientific contact	Luke Howard, Luke Howard, l.howard@imperial.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	12 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2017
Global end of trial reached?	Yes
Global end of trial date	22 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical value of using intravenous iron (ferric carboxymaltose) infusion in iron deficient patients with idiopathic pulmonary arterial hypertension.

The primary endpoint will be endurance time at the end of endurance bicycle cardiopulmonary exercise testing at 80% peak work rate determined from the baseline incremental exercise test, measured at 12 weeks after study treatment.

Protection of trial subjects:	
All adverse events were monitored and recorded throughout the trial. No other specific protection.	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 March 2011
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 Kingdom: 34
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	34

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients participating in this study are adult males and females with symptomatic IPAH as defined by the eligibility criteria specified in the protocol.

Pre-assignment

Screening details:

Potential participants will be screened using data collected during their routine outpatient appointment at the Pulmonary Hypertension Service or PH Clinic. Any unavailable or missing data will be collected at the screening visit (week 0) once the patient has provided written informed consent.

Pre-assignment period milestones

Number of subjects started	39
Number of subjects completed	39

Period 1

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

Arms

Arm title	All patients

Arm description:

There are no products specified, as this is the baseline period, prior to randomisation.

Arm type	Baseline: no intervention
Investigational medicinal product name	Ferinject
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg Ferinject, intravenous infusion

Number of subjects in period 1	All patients
Started	39
Completed	39

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Active treatment: Ferinject

Arm description:

1000mg Ferinject infused over 15 minutes

Arm type	Experimental
Investigational medicinal product name	Ferinject
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg Ferinject, intravenous infusion

Arm title	Placebo: Saline

Arm description:

Saline infused over 15 minutes

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

Dosage and administration details:

1000ml saline for intravenous infusion

Number of subjects in period 2	Active treatment: Ferinject	Placebo: Saline
Started	39	39
Completed	39	39

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	39	39	
Age categorical			
All participants			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	34	34	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	29	29	
Male	10	10	

Subject analysis sets

Subject analysis set title	Total population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants

Reporting group values	Total population		
Number of subjects	39		
Age categorical			
All participants			
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)	34		
From 65-84 years	5		
85 years and over	0		

Gender categorical Units: Subjects			
Female	29		
Male	10		

End points

End points reporting groups

Reporting group title	All patients
Reporting group description:	
There are no products specified, as this is the baseline period, prior to randomisation.	
Reporting group title	Active treatment: Ferinject
Reporting group description:	
1000mg Ferinject infused over 15 minutes	
Reporting group title	Placebo: Saline
Reporting group description:	
Saline infused over 15 minutes	
Subject analysis set title	Total population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants	

Primary: Endurance time from start to finish of Cardio-pulmonary exercise test

End point title	Endurance time from start to finish of Cardio-pulmonary exercise test
End point description:	
End point type	Primary
End point timeframe:	
12 weeks post treatment	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: seconds				
arithmetic mean (confidence interval 95%)	315.44 (274.68 to 356.20)	302.89 (260.09 to 345.69)		

Statistical analyses

Statistical analysis title	Linear mixed model
Statistical analysis description:	
All primary and secondary efficacy endpoints were analysed using linear mixed models appropriate for a crossover design. The linear models included administration sequence, period and treatment as fixed effects and subject as a random effect, and all models included relevant and statistically significant baseline covariates.	
Comparison groups	Active treatment: Ferinject v Placebo: Saline

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7109
Method	Mixed models analysis

Secondary: Peak VO2 Level at 12 Weeks After Study Treatment

End point title	Peak VO2 Level at 12 Weeks After Study Treatment

End point description:

End point type	Secondary

End point timeframe:

12 weeks post study treatment

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: litres per minute				
arithmetic mean (confidence interval 95%)	1.17 (1.10 to 1.22)	1.13 (1.08 to 1.21)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6583
Method	Mixed models analysis

Secondary: VO2 at Metabolic Threshold

End point title	VO2 at Metabolic Threshold

End point description:

End point type	Secondary

End point timeframe:

12 weeks post study treatment

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: litres per minute				
arithmetic mean (confidence interval 95%)	0.78 (0.73 to 0.82)	0.77 (0.73 to 0.82)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9773
Method	Mixed models analysis

Secondary: VE/VCO2 Slope

End point title	VE/VCO2 Slope
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: interger				
arithmetic mean (confidence interval 95%)	41.15 (39.43 to 42.43)	42.35 (40.58 to 44.07)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1815
Method	Mixed models analysis

Secondary: VO2 / WR Slope

End point title	VO2 / WR Slope

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: integer				
arithmetic mean (confidence interval 95%)	8.12 (7.50 to 8.71)	8.04 (7.46 to 8.68)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8751
Method	Mixed models analysis

Secondary: Peak O2 Pulse Rate

End point title	Peak O2 Pulse Rate

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: interger				
arithmetic mean (confidence interval 95%)	8.83 (8.36 to 9.28)	8.62 (8.17 to 9.08)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4813
Method	Mixed models analysis

Secondary: VO2 at the End of Endurance Cardio-pulmonary Exercise Test

End point title	VO2 at the End of Endurance Cardio-pulmonary Exercise Test
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: litres per minute				
least squares mean (confidence interval 95%)	4.25 (3.5 to 5.01)	4.49 (3.71 to 5.28)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2395
Method	Mixed models analysis

Secondary: VO2 at 3 mins

End point title	VO2 at 3 mins
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: integer				
least squares mean (confidence interval 95%)	1.29 (0.98 to 1.60)	1.14 (0.81 to 1.48)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4758
Method	Mixed models analysis

Secondary: Iron Indices: Serum Iron

End point title	Iron Indices: Serum Iron
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: umol/l				
arithmetic mean (confidence interval 95%)	17.15 (15.42 to 18.64)	15.48 (13.94 to 17.17)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2002
Method	Mixed models analysis

Secondary: Iron Indices: Transferrin Saturations

End point title	Iron Indices: Transferrin Saturations
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: percentage				
arithmetic mean (confidence interval 95%)	26.2 (22.96 to 28.89)	22 (19.21 to 25.12)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0727
Method	Mixed models analysis

Secondary: Iron Indices: Ferritin

End point title	Iron Indices: Ferritin
End point description:	

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: ug/L				
arithmetic mean (confidence interval 95%)	150.32 (118.63 to 175.51)	92.74 (66.08 to 122.88)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis

Secondary: Iron Indices: sTfR

End point title	Iron Indices: sTfR
End point description:	

End point type	Secondary

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: nmol/L				
arithmetic mean (confidence interval 95%)	28.37 (25.73 to 31.72)	37.25 (34.02 to 40.0)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis

Secondary: 6 minute walk test: Distance Walked

End point title	6 minute walk test: Distance Walked
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: metres				
arithmetic mean (confidence interval 95%)	426.03 (411.57 to 440.20)	424.3 (410.06 to 438.70)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8093
Method	Mixed models analysis

Secondary: 6 minute walk test: Borg dyspnoea score after test

End point title	6 minute walk test: Borg dyspnoea score after test
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	3.24 (2.75 to 3.75)	3.68 (3.18 to 4.17)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Placebo: Saline v Active treatment: Ferinject
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0862
Method	Mixed models analysis

Secondary: Iron Indices: NT-pro-BNP

End point title	Iron Indices: NT-pro-BNP
End point description:	
End point type	Secondary

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: fmol/ml				
arithmetic mean (confidence interval 95%)	307.64 (186.47 to 437.62)	424.37 (297.52 to 548.39)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1041
Method	Mixed models analysis

Secondary: Quality of Life: CAMPHOR Activity Score

End point title	Quality of Life: CAMPHOR Activity Score
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	9.12 (8.14 to 10.07)	9.18 (8.25 to 10.16)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8948
Method	Mixed models analysis

Secondary: Quality of Life: CAMPHOR Symptom Score

End point title	Quality of Life: CAMPHOR Symptom Score
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Items on a scale				
arithmetic mean (confidence interval 95%)	7.94 (6.99 to 8.89)	7.94 (7.02 to 8.89)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9559
Method	Mixed models analysis

Secondary: Quality of Life: CAMPHOR QoL Score

End point title	Quality of Life: CAMPHOR QoL Score
End point description:	

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Items on a scale				
arithmetic mean (confidence interval 95%)	7.58 (6.38 to 8.69)	7 (5.91 to 8.16)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2423
Method	Mixed models analysis

Secondary: Mean Right Atrial Pressure

End point title	Mean Right Atrial Pressure

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: TBC				
arithmetic mean (confidence interval 95%)	6.56 (5.40 to 9.23)	10.12 (7.17 to 11.21)		

Statistical analyses

Statistical analysis title	Linear mixed method
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1221
Method	Mixed models analysis

Secondary: Peak VO2 Level in ml/min/kg

End point title	Peak VO2 Level in ml/min/kg
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: ml/min/kg				
arithmetic mean (confidence interval 95%)	15.10 (14.10 to 15.58)	14.67 (14.20 to 15.68)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7625
Method	Mixed models analysis

Secondary: VO2 at Metabolic Threshold measured during incremental CPET

End point title	VO2 at Metabolic Threshold measured during incremental CPET
End point description:	

End point type	Secondary
End point timeframe:	
12 weeks post study treatment	

End point values	Active treatment: Ferinject	Placebo: Saline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: ml/min/kg				
arithmetic mean (confidence interval 95%)	10.01 (9.45 to 10.46)	9.99 (9.52 to 10.53)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Active treatment: Ferinject v Placebo: Saline
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7711
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
From consent to 24 weeks	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	All participants

Reporting group description: -

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 39 (20.51%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hypophosphataemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal haematoma			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tonsilitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)		
Investigations			
Hypophosphataemia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	6		
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	10		

Headache			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Cough			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Infections and infestations			

Cold			
subjects affected / exposed	8 / 39 (20.51%)		
occurrences (all)	11		
Respiratory Infection			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Flu symptoms			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2011	Change to eligibility criteria, separate patient documents for participating sites.
02 July 2012	Change inclusion criterion 3, change of PI at one participating site.
04 December 2012	Addition of fasting glucose and insulin measurements.
24 September 2013	Change of PI at participating site
20 March 2014	Changes to eligibility, reduction in number of protocol clinic visits, removal of week 36 visit and addition of activity monitor.
25 June 2015	Changes to cardiac cath, activity monitor and replacement of visits 2 and 4 with telephone calls.
14 December 2015	Addition of German site.

Notes:

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.

Pt 2003, 3004, 4002-05 had endurance CPETs performed at incorrect workloads, so those data were replaced by imputed values. Visit 5 CPETs for 1008, 1018 and 1019 were outside protocol window. 1014 received placebo at both treatment visits in error

Notes: