Clinical trial results:
A Phase 3, double-blind, multicenter, placebo-controlled study of PledOx used on top of modified FOLFOX6 (5 FU/FA and Oxaliplatin) to prevent chemotherapy induced peripheral neuropathy (CIPN) in patients with first-line metastatic colorectal cancer

Summary

EudraCT number	2017-004754-42
Trial protocol	GB BE DE FR ES HU IT
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	16 September 2021
First version publication date	16 September 2021

Trial information

Trial identification

Sponsor protocol code	PP06490

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03654729
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Egetis Therapeutics AB (formerly PledPharma AB)
Sponsor organisation address	Egetis Therapeutics AB Klara Norra Kyrkogata 26 , Stockholm , Sweden, SE 111 22 Stockholm
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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	11 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare each dose of PledOx (2 and 5 µmol/kg) vs placebo with respect to the proportion of subjects with moderate or severe chronic CIPN

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. An independent Data Monitoring Committee monitored accumulating safety, efficacy and other types of data throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2018
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	Belgium: 23
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Japan: 84
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	291
EEA total number of subjects	130

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)	154
From 65 to 84 years	136
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited in the US, EU and Asia between 2018 and 1 March 2020.

Pre-assignment

Screening details:

386 subjects were screened in the 28 days before the start of treatment, 291 were randomised and 285 were were treated. The study was prematurely terminated and enrolled patients were followed until the data cut-off date of 31 August 2020; these patients have been assigned as "completed" in the disposition.

Period 1

Period 1 title	Subjects randomised
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PledOx (2 µmol/kg)

Arm description:

Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Calmangafodipir (2 µmol/kg)
Investigational medicinal product code	
Other name	PledOx
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

PledOx 2 µmol/kg + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Arm title	PledOx (5 µmol/kg)

Arm description:

Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Calmangafodipir (5 µmol/kg)
Investigational medicinal product code	
Other name	PledOx
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

PledOx 5 µmol/kg + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Arm title	Placebo

Arm description:

Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Placebo

Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Number of subjects in period 1	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo
Started	97	96	98
Completed	96	93	96
Not completed	1	3	2
Physician decision	1	-	-
Consent withdrawn by subject	-	1	-
Unknown	-	2	2

Period 2	
Period 2 title	Subjects treated
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PledOx (2 µmol/kg)

Arm description:

Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Calmangafodipir (2 µmol/kg)
Investigational medicinal product code	
Other name	PledOx
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

PledOx 2 µmol/kg + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Arm title	PledOx (5 µmol/kg)

Arm description:

Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Experimental

Investigational medicinal product name	Calmangafodipir (5 µmol/kg)
Investigational medicinal product code	
Other name	PledOx
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

PledOx 5 µmol/kg + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Arm title	Placebo

Arm description:

Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo + mFOLFOX6 chemotherapy administered every 2 weeks (±2 days) for 12 cycles

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: There were six subjects randomised who were not treated. The baseline period represents subjects who were treated and the baseline data are presented for the subjects treated.

Number of subjects in period 2[2]	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo
Started	96	93	96
Completed	66	70	69
Not completed	30	23	27
Consent withdrawn by subject	8	5	4
Physician decision	1	-	-
Study terminated by Sponsor	3	5	4
Death	9	9	16
Unknown	2	2	3
Non-compliance with study drug	-	1	-
Lost to follow-up	2	-	-
Progressive disease	3	-	-
Site terminated by Sponsor	1	-	-
Protocol deviation	1	1	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There were six subjects randomised who were not treated. The baseline period represents subjects who were treated and the baseline data are presented for the subjects treated.

Baseline characteristics

Reporting groups	
Reporting group title	PledOx (2 µmol/kg)
Reporting group description:	
Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	

Reporting group title	PledOx (5 µmol/kg)
Reporting group description:	
Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	
Reporting group title	Placebo
Reporting group description:	
Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	

Reporting group values	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo
Number of subjects	96	93	96
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)	48	52	51
From 65-84 years	47	41	45
85 years and over	1	0	0
Age continuous Units: years			
arithmetic mean	63.5	62.9	61.6
standard deviation	± 10.5	± 9.6	± 12.4
Gender categorical Units: Subjects			
Female	36	43	40
Male	60	50	56
Race Units: Subjects			
Asian	41	40	39
Black or African American	0	1	1
Unknown	6	7	5
White	49	45	51
ECOG baseline status Units: Subjects			
Score 0	65	62	53
Score 1	31	31	41

Unknown	0	0	2

Reporting group values	Total		
Number of subjects	285		
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)	151		
From 65-84 years	133		
85 years and over	1		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	119		
Male	166		
Race Units: Subjects			
Asian	120		
Black or African American	2		
Unknown	18		
White	145		
ECOG baseline status Units: Subjects			
Score 0	180		
Score 1	103		
Unknown	2		

End points

End points reporting groups

Reporting group title	PledOx (2 µmol/kg)

Reporting group description:

Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Reporting group title	PledOx (5 µmol/kg)

Reporting group description:

Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Reporting group title	Placebo

Reporting group description:

Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Reporting group title	PledOx (2 µmol/kg)

Reporting group description:

Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Reporting group title	PledOx (5 µmol/kg)

Reporting group description:

Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Reporting group title	Placebo

Reporting group description:

Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.

Primary: Moderate or severe chronic chemotherapy induced peripheral neuropathy (CIPN)

End point title	Moderate or severe chronic chemotherapy induced peripheral neuropathy (CIPN)

End point description:

Proportion of subjects (with moderate or severe chronic CIPN) scoring 3 or 4 in at least 1 of the first 4 items of the FACT/GOG-NTX-13 (i.e., FACT/GOG-NTX-4), targeting numbness, tingling or discomfort in hands and/or feet, 9 months after the first dose of IMP (i.e. PledOx or placebo administered on Day 1, Cycle 1 of mFOLFOX6 chemotherapy).

End point type	Primary

End point timeframe:

9 months

End point values	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	55	57	
Units: Number of patients	31	27	25	

Statistical analyses

Statistical analysis title	PledOx (2 µmol/kg) versus Placebo
Comparison groups	PledOx (2 µmol/kg) v Placebo
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2266
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.3842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8172
upper limit	2.3446

Statistical analysis title	PledOx (5 µmol/kg) versus Placebo
Statistical analysis description:	
Cochran-Mantel-Haenszel estimate of the common relative risk of moderate to severe CIPN.	
Comparison groups	PledOx (5 µmol/kg) v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7434
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.0951
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6356
upper limit	1.887

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival defined as time from randomisation until progressive disease (according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) or death from any cause.

End point type	Secondary

End point timeframe:

12 and 24 months; analysis performed based on available data at cut-off 31 August 2020

End point values	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	93	95	
Units: Number of events	40	36	36	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival defined as time from randomisation to death from any cause. If the subject was alive at the end of the follow-up period (or was lost to follow-up), the subject was censored on the last date the subject was known to be alive.

End point type	Secondary

End point timeframe:

36 months; analysis performed based on available data at cut-off 31 August 2020

End point values	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	93	95	
Units: Number of events	9	9	16	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening until 30 days after the end of treatment visit which occurred after up to 6 months of treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	PledOx (2 µmol/kg)
Reporting group description:	
Calmangafodipir [PledOx] (2 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	
Reporting group title	PledOx (5 µmol/kg)
Reporting group description:	
Calmangafodipir [PledOx] (5 µmol/kg) on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	
Reporting group title	Placebo
Reporting group description:	
Placebo on day 1 every 2 weeks to subjects as an intravenous infusion, combined with mFOLFOX6 chemotherapy.	

Serious adverse events	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 96 (28.13%)	21 / 93 (22.58%)	24 / 96 (25.00%)
number of deaths (all causes)	9	9	16
number of deaths resulting from adverse events	2	3	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour perforation			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			

subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Euthanasia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			

subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 96 (2.08%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian vein thrombosis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 96 (0.00%)	3 / 93 (3.23%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract stoma complication			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiogenic shock			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			

Altered state of consciousness			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 96 (0.00%)	2 / 93 (2.15%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 96 (0.00%)	2 / 93 (2.15%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 96 (2.08%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 96 (1.04%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 96 (2.08%)	0 / 93 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nausea			
subjects affected / exposed	2 / 96 (2.08%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 96 (3.13%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Device related infection			
subjects affected / exposed	2 / 96 (2.08%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 96 (1.04%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			

subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	2 / 96 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneunonia			
subjects affected / exposed	1 / 96 (1.04%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 93 (0.00%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 96 (0.00%)	1 / 93 (1.08%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 96 (1.04%)	1 / 93 (1.08%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 96 (0.00%)	0 / 93 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 96 (0.00%)	3 / 93 (3.23%)	0 / 96 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PledOx (2 µmol/kg)	PledOx (5 µmol/kg)	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 96 (96.88%)	91 / 93 (97.85%)	95 / 96 (98.96%)
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 96 (12.50%)	11 / 93 (11.83%)	12 / 96 (12.50%)
occurrences (all)	12	16	16
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 96 (14.58%)	17 / 93 (18.28%)	21 / 96 (21.88%)
occurrences (all)	23	47	41
Fatigue			
subjects affected / exposed	25 / 96 (26.04%)	23 / 93 (24.73%)	23 / 96 (23.96%)
occurrences (all)	38	33	35
Malaise			
subjects affected / exposed	6 / 96 (6.25%)	4 / 93 (4.30%)	9 / 96 (9.38%)
occurrences (all)	6	5	10
Oedema peripheral			
subjects affected / exposed	6 / 96 (6.25%)	3 / 93 (3.23%)	4 / 96 (4.17%)
occurrences (all)	8	3	5
Pyrexia			
subjects affected / exposed	12 / 96 (12.50%)	8 / 93 (8.60%)	9 / 96 (9.38%)
occurrences (all)	15	11	10
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	5 / 96 (5.21%)	2 / 93 (2.15%)	5 / 96 (5.21%)
occurrences (all)	6	2	5
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 96 (4.17%)	6 / 93 (6.45%)	6 / 96 (6.25%)
occurrences (all)	4	7	6
Dyspnoea			
subjects affected / exposed	3 / 96 (3.13%)	4 / 93 (4.30%)	5 / 96 (5.21%)
occurrences (all)	3	4	6
Epistaxis			
subjects affected / exposed	13 / 96 (13.54%)	14 / 93 (15.05%)	9 / 96 (9.38%)
occurrences (all)	18	15	13
Hiccups			
subjects affected / exposed	4 / 96 (4.17%)	3 / 93 (3.23%)	5 / 96 (5.21%)
occurrences (all)	10	6	6
Oropharyngeal pain			
subjects affected / exposed	2 / 96 (2.08%)	5 / 93 (5.38%)	2 / 96 (2.08%)
occurrences (all)	3	5	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 96 (5.21%)	3 / 93 (3.23%)	5 / 96 (5.21%)
occurrences (all)	5	3	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 96 (5.21%)	7 / 93 (7.53%)	8 / 96 (8.33%)
occurrences (all)	5	8	16
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 96 (6.25%)	7 / 93 (7.53%)	7 / 96 (7.29%)
occurrences (all)	7	8	16
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 96 (0.00%)	5 / 93 (5.38%)	6 / 96 (6.25%)
occurrences (all)	0	5	8
Dysgeusia			
subjects affected / exposed	16 / 96 (16.67%)	20 / 93 (21.51%)	21 / 96 (21.88%)
occurrences (all)	18	23	24
Headache			
subjects affected / exposed	7 / 96 (7.29%)	7 / 93 (7.53%)	5 / 96 (5.21%)
occurrences (all)	10	7	6

Neuropathy peripheral			
subjects affected / exposed	32 / 96 (33.33%)	33 / 93 (35.48%)	36 / 96 (37.50%)
occurrences (all)	89	84	74
Paraesthesia			
subjects affected / exposed	17 / 96 (17.71%)	15 / 93 (16.13%)	18 / 96 (18.75%)
occurrences (all)	26	25	35
Peripheral sensory neuropathy			
subjects affected / exposed	42 / 96 (43.75%)	40 / 93 (43.01%)	42 / 96 (43.75%)
occurrences (all)	86	79	97
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 96 (11.46%)	8 / 93 (8.60%)	14 / 96 (14.58%)
occurrences (all)	17	15	23
Leukopenia			
subjects affected / exposed	12 / 96 (12.50%)	10 / 93 (10.75%)	14 / 96 (14.58%)
occurrences (all)	29	22	26
Neutropenia			
subjects affected / exposed	40 / 96 (41.67%)	48 / 93 (51.61%)	37 / 96 (38.54%)
occurrences (all)	91	97	90
Thrombocytopenia			
subjects affected / exposed	12 / 96 (12.50%)	16 / 93 (17.20%)	16 / 96 (16.67%)
occurrences (all)	26	28	36
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 96 (16.67%)	14 / 93 (15.05%)	16 / 96 (16.67%)
occurrences (all)	21	21	18
Abdominal pain upper			
subjects affected / exposed	5 / 96 (5.21%)	4 / 93 (4.30%)	5 / 96 (5.21%)
occurrences (all)	5	5	6
Constipation			
subjects affected / exposed	24 / 96 (25.00%)	15 / 93 (16.13%)	14 / 96 (14.58%)
occurrences (all)	26	17	19
Diarrhoea			
subjects affected / exposed	32 / 96 (33.33%)	27 / 93 (29.03%)	41 / 96 (42.71%)
occurrences (all)	56	37	68
Dyspepsia			

subjects affected / exposed	8 / 96 (8.33%)	6 / 93 (6.45%)	4 / 96 (4.17%)
occurrences (all)	10	7	4
Nausea			
subjects affected / exposed	34 / 96 (35.42%)	42 / 93 (45.16%)	47 / 96 (48.96%)
occurrences (all)	67	69	82
Stomatitis			
subjects affected / exposed	29 / 96 (30.21%)	24 / 93 (25.81%)	29 / 96 (30.21%)
occurrences (all)	39	41	43
Vomiting			
subjects affected / exposed	11 / 96 (11.46%)	16 / 93 (17.20%)	20 / 96 (20.83%)
occurrences (all)	24	32	30
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 96 (9.38%)	11 / 93 (11.83%)	13 / 96 (13.54%)
occurrences (all)	9	14	13
Dermatitis acneiform			
subjects affected / exposed	9 / 96 (9.38%)	7 / 93 (7.53%)	10 / 96 (10.42%)
occurrences (all)	15	8	18
Dry skin			
subjects affected / exposed	9 / 96 (9.38%)	11 / 93 (11.83%)	4 / 96 (4.17%)
occurrences (all)	9	11	7
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 96 (7.29%)	4 / 93 (4.30%)	6 / 96 (6.25%)
occurrences (all)	10	6	6
Rash			
subjects affected / exposed	6 / 96 (6.25%)	19 / 93 (20.43%)	14 / 96 (14.58%)
occurrences (all)	13	30	18
Skin fissures			
subjects affected / exposed	1 / 96 (1.04%)	5 / 93 (5.38%)	1 / 96 (1.04%)
occurrences (all)	2	7	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 96 (5.21%)	1 / 93 (1.08%)	2 / 96 (2.08%)
occurrences (all)	6	1	2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 96 (5.21%)	4 / 93 (4.30%)	6 / 96 (6.25%)
occurrences (all)	5	5	8
Muscle spasms			
subjects affected / exposed	1 / 96 (1.04%)	6 / 93 (6.45%)	4 / 96 (4.17%)
occurrences (all)	1	9	4
Myalgia			
subjects affected / exposed	3 / 96 (3.13%)	2 / 93 (2.15%)	10 / 96 (10.42%)
occurrences (all)	3	2	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 96 (4.17%)	4 / 93 (4.30%)	5 / 96 (5.21%)
occurrences (all)	5	5	5
Paronychia			
subjects affected / exposed	2 / 96 (2.08%)	7 / 93 (7.53%)	8 / 96 (8.33%)
occurrences (all)	3	8	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	30 / 96 (31.25%)	26 / 93 (27.96%)	27 / 96 (28.13%)
occurrences (all)	47	33	42
Hypoalbuminaemia			
subjects affected / exposed	5 / 96 (5.21%)	1 / 93 (1.08%)	2 / 96 (2.08%)
occurrences (all)	6	3	3
Hypokalaemia			
subjects affected / exposed	3 / 96 (3.13%)	7 / 93 (7.53%)	9 / 96 (9.38%)
occurrences (all)	5	11	17
Hypomagnesaemia			
subjects affected / exposed	5 / 96 (5.21%)	7 / 93 (7.53%)	5 / 96 (5.21%)
occurrences (all)	5	8	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2018	• Added more rationale for the 2 µmol/kg dose • Amended contraceptive measures • Pregnancy added as a criterion for Investigational Medicinal Product (IMP) discontinuation • Amended the schedule for the Month 3 and Month 6 Assessment Visits • Added time points for assessing health economic impact • Added clarity over when computed tomography (CT)/magnetic resonance imaging (MRI) scans should be performed. Removed CT/MRI assessment at Treatment Visit 12. • Clarified that "graduated tuning fork" referred to the vibration sensitivity test.
20 February 2018	• Increased the duration of contraception after the completion of study therapy • Removed 'Australia' from the protocol, as the study was not to be conducted there • Amended the volume of blood collected for manganese evaluations
20 June 2018	• Updated text to include Asian centres in the study • Included input regarding pregnancy from Competent Authorities into the protocol text • Updated information on the use of background therapy
12 September 2018	• Adjusted the number of subjects included in the pharmacokinetic (PK) and electrocardiogram (ECG) examinations. • Included input from the US Food and Drug Administration (FDA) to the protocol text • Updated background information.
09 July 2019	• Added conversion and maintenance strategy during the Treatment Phase • Added region and PK sub-study as stratification factors to randomization • Updated exclusion criteria to exclude subjects with resectable metastatic disease and to add an exception for hepatitis B virus (HBV) infection • Clarified study procedures and timing in relation to assessments during Screening, Treatment, and Follow-up Phases • Clarified blinding procedures, IMP storage requirements, and IMP destruction guide • Removed the 8-hour time point from PK assessment • Specified that adverse events will be collected after signing the informed consent form

09 January 2020	• Updated exclusion criteria to exclude subjects with any history of seizures • Updated infusion duration for PledOx/placebo • Updated potential risks according to recently reported serious adverse events (SAEs) • Clarified DSMB review requirement for adverse events/SAEs of seizures, anaphylactoid reactions, and allergic infusion reactions • Clarified stopping criteria for subjects with seizures • Added details for premedications before PledOx/placebo infusion • Clarified procedures to be followed in case a death is an outcome of an event • Clarified PledOx-related adverse events • Specified the situations that trigger a brain MRI investigation and a neurological examination • Updated the flow chart of monitoring increased manganese level and/or Parkinson-like symptoms
15 May 2020	The rationale for this amendment was to update the protocol regarding the decision to prematurely terminate the study and to include changes resulting from the COVID-19 pandemic and associated site/country restrictions. • Updated study duration with implementation of an estimated data cut-off date by 30 Sep 2020 • Discontinuation of IMP, screening and randomization of patients, PK assessments, ECG measurements, and serum β-HCG pregnancy tests • Discontinuation of blood manganese samples with the exception of patients with Parkinson-like symptoms • Continuation of study visits as originally planned but without dosing of IMP • Collection of adverse events and concomitant medications up to 30 days after the end of treatment visit and until resolution • Collection of overall survival data until the estimated data cut-off date by 30 Sep 2020 • Added an option for remote data collection during the COVID-19 pandemic for some assessments, according to local requirements • Amended statistical section, making reference to the updated statistical analysis plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 March 2020	On 23 January 2020, the Sponsor announced that the United States (US) Food and Drug Administration (FDA) had issued a clinical hold in the US of the POLAR program. The implication was that recruitment and dosing of patients in the POLAR-M study was halted in the US. On 01 March 2020, the Sponsor decided to place recruitment and dosing of patients in the POLAR program on hold. The decision followed interactions with the French regulatory authority, ANSM and the US clinical hold. As of 02 March 2020, no investigational medicinal product (IMP) was administered and no more patients were enrolled. Enrolled patients continued to be followed until the data cut-off date of 31 August 2020.	-

Notes:

Limitations and caveats

None reported