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 the adjuvant treatment of patients with Stage III or high-risk Stage II colorectal cancer

Summary

EudraCT number	2017-004707-43
Trial protocol	BE FR DE GB ES 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	PP06489

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04034355
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Egetis Therapeutics AB (formerly PledPharma AB)
Sponsor organisation address	Klara Norra Kyrkogata 26, Stockholm, Sweden, SE 111 22
Public contact	Kristina Sjöblom Nygren, CMO, Head Clinical Development, Egetis Therapeutics AB , +46 732344698, kristina.sjoblom@egetis.com
Scientific contact	Kristina Sjöblom Nygren, CMO, Head Clinical Development, Egetis Therapeutics AB , +46 732344698, kristina.sjoblom@egetis.com

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 PledOx (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 January 2019
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: 64
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Japan: 53
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Taiwan: 6
Worldwide total number of subjects	301
EEA total number of subjects	204

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)	150
From 65 to 84 years	150
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in the EU and Asia between 2018 and 1 March 2020.

Pre-assignment

Screening details:

371 subjects were screened in the 28 days before the start of treatment, 301 were randomised and 297 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	Randomised subjects
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 (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	Intravenous use

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	Sodium Chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

Number of subjects in period 1	PledOx (5 µmol/kg)	Placebo
Started	151	150
Completed	147	150
Not completed	4	0
Consent withdrawn by subject	3	-
Unknown	1	-

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 (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	Intravenous use

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	Sodium Chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

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 four 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 (5 µmol/kg)	Placebo
Started	147	150
Completed	117	115
Not completed	30	35
Physician decision	1	-
Consent withdrawn by subject	9	11
Study terminated by Sponsor	10	17
Adverse event, non-fatal	2	-
Death	1	1
Unknown	1	-
Lost to follow-up	1	-
Progressive disease	1	-
Site terminated by Sponsor	4	5
Protocol deviation	-	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 four 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 (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 (5 µmol/kg)	Placebo	Total
Number of subjects	147	150	297
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)	74	75	149
From 65-84 years	72	75	147
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	63.3	62.4	
standard deviation	± 10.4	± 10.2	-
Gender categorical Units: Subjects			
Female	69	61	130
Male	78	89	167
Race Units: Subjects			
Asian	43	43	86
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	1	0	1
Other or Unknown	15	14	29
White	87	93	180
ECOG Performance Status Units: Subjects			
Score 0	118	122	240
Score 1	29	28	57

End points

End points reporting groups

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 (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 investigational medicinal product (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 (5 µmol/kg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	119		
Units: participants	68	46		

Statistical analyses

Statistical analysis title	PledOx (5 µmol/kg) versus Placebo
Comparison groups	PledOx (5 µmol/kg) v Placebo

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.521
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.0462
upper limit	2.2113

Secondary: Disease free survival

End point title	Disease free survival

End point description:

Disease-free survival defined as the time from the date of randomisation until the date of objectively determined signs or symptoms of recurrence of colorectal cancer (CRC) or death due to any cause.

End point type	Secondary

End point timeframe:

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

End point values	PledOx (5 µmol/kg)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	150		
Units: Number of events	7	15		

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 (5 µmol/kg)
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	PledOx (5 µmol/kg)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 147 (13.61%)	20 / 150 (13.33%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Administration site cellulitis			

subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 147 (1.36%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 147 (2.04%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pharyngeal inflammation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 147 (1.36%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device extrusion			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (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			
Gastrointestinal stoma complication			

subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			

subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 147 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis acute			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
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	1 / 147 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (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			
Clostridium difficile infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 147 (0.68%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	PledOx (5 µmol/kg)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 147 (99.32%)	146 / 150 (97.33%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 147 (7.48%)	8 / 150 (5.33%)	
occurrences (all)	16	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 147 (21.77%)	36 / 150 (24.00%)	
occurrences (all)	87	73	
Fatigue			
subjects affected / exposed	39 / 147 (26.53%)	36 / 150 (24.00%)	
occurrences (all)	61	78	
Malaise			
subjects affected / exposed	8 / 147 (5.44%)	7 / 150 (4.67%)	
occurrences (all)	23	9	
Pyrexia			
subjects affected / exposed	10 / 147 (6.80%)	13 / 150 (8.67%)	
occurrences (all)	13	18	
Immune system disorders			
Infusion related reaction			
subjects affected / exposed	8 / 147 (5.44%)	2 / 150 (1.33%)	
occurrences (all)	9	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 147 (4.76%)	13 / 150 (8.67%)	
occurrences (all)	7	14	
Epistaxis			
subjects affected / exposed	12 / 147 (8.16%)	12 / 150 (8.00%)	
occurrences (all)	14	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 147 (5.44%)	3 / 150 (2.00%)	
occurrences (all)	8	3	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	11 / 147 (7.48%)	17 / 150 (11.33%)	
occurrences (all)	18	26	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 147 (7.48%)	15 / 150 (10.00%)	
occurrences (all)	19	23	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 147 (7.48%)	4 / 150 (2.67%)	
occurrences (all)	14	4	
Dysaesthesia			
subjects affected / exposed	7 / 147 (4.76%)	13 / 150 (8.67%)	
occurrences (all)	15	22	
Dysgeusia			
subjects affected / exposed	35 / 147 (23.81%)	34 / 150 (22.67%)	
occurrences (all)	43	47	
Headache			
subjects affected / exposed	12 / 147 (8.16%)	13 / 150 (8.67%)	
occurrences (all)	14	18	
Neuropathy peripheral			
subjects affected / exposed	67 / 147 (45.58%)	73 / 150 (48.67%)	
occurrences (all)	187	217	
Paraesthesia			
subjects affected / exposed	30 / 147 (20.41%)	33 / 150 (22.00%)	
occurrences (all)	82	98	
Peripheral sensory neuropathy			
subjects affected / exposed	49 / 147 (33.33%)	39 / 150 (26.00%)	
occurrences (all)	132	129	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 147 (11.56%)	17 / 150 (11.33%)	
occurrences (all)	24	20	
Leukopenia			
subjects affected / exposed	18 / 147 (12.24%)	19 / 150 (12.67%)	
occurrences (all)	34	40	
Neutropenia			

subjects affected / exposed	62 / 147 (42.18%)	68 / 150 (45.33%)	
occurrences (all)	144	203	
Thrombocytopenia			
subjects affected / exposed	46 / 147 (31.29%)	58 / 150 (38.67%)	
occurrences (all)	69	134	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 147 (5.44%)	15 / 150 (10.00%)	
occurrences (all)	9	21	
Abdominal pain			
subjects affected / exposed	13 / 147 (8.84%)	14 / 150 (9.33%)	
occurrences (all)	18	18	
Constipation			
subjects affected / exposed	30 / 147 (20.41%)	25 / 150 (16.67%)	
occurrences (all)	38	39	
Diarrhoea			
subjects affected / exposed	59 / 147 (40.14%)	56 / 150 (37.33%)	
occurrences (all)	120	90	
Dry mouth			
subjects affected / exposed	4 / 147 (2.72%)	9 / 150 (6.00%)	
occurrences (all)	4	9	
Dyspepsia			
subjects affected / exposed	10 / 147 (6.80%)	11 / 150 (7.33%)	
occurrences (all)	10	13	
Nausea			
subjects affected / exposed	88 / 147 (59.86%)	69 / 150 (46.00%)	
occurrences (all)	193	155	
Stomatitis			
subjects affected / exposed	50 / 147 (34.01%)	31 / 150 (20.67%)	
occurrences (all)	67	37	
Vomiting			
subjects affected / exposed	27 / 147 (18.37%)	27 / 150 (18.00%)	
occurrences (all)	33	34	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	23 / 147 (15.65%)	18 / 150 (12.00%)	
occurrences (all)	25	19	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	11 / 147 (7.48%)	15 / 150 (10.00%)	
occurrences (all)	29	21	
Rash			
subjects affected / exposed	8 / 147 (5.44%)	5 / 150 (3.33%)	
occurrences (all)	8	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 147 (6.12%)	2 / 150 (1.33%)	
occurrences (all)	11	3	
Muscle spasms			
subjects affected / exposed	9 / 147 (6.12%)	6 / 150 (4.00%)	
occurrences (all)	12	6	
Pain in extremity			
subjects affected / exposed	8 / 147 (5.44%)	2 / 150 (1.33%)	
occurrences (all)	10	2	
Pain in jaw			
subjects affected / exposed	5 / 147 (3.40%)	8 / 150 (5.33%)	
occurrences (all)	8	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 147 (5.44%)	7 / 150 (4.67%)	
occurrences (all)	8	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 147 (28.57%)	37 / 150 (24.67%)	
occurrences (all)	66	62	
Hypokalaemia			
subjects affected / exposed	3 / 147 (2.04%)	11 / 150 (7.33%)	
occurrences (all)	5	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2018	• Updated text to include Asian centers in the study • Included input from Competent Authorities into the protocol text • Updated information on the use of background therapy
27 September 2018	• Included input from the United States Food and Drug Administration (FDA) • Updated background information
12 July 2019	• Updated exclusion criteria to add 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, Investigational Medicinal Product (IMP) storage requirements, and IMP destruction guide • 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 IDMC review requirement for adverse events/SAEs of seizures, anaphylactoid reactions, and allergic infusion reaction • Clarified stopping criteria for subjects with seizures • Added details for pre-medications 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 magnetic resonance imaging (MRI) investigation and a neurological examination • Updated the flow chart of monitoring increased manganese level and/or Parkinson-like symptoms
15 May 2020	To update the protocol regarding the decision to prematurely terminate the study as well as 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 randomisation 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 AEs 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 updated statistical analysis plan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 March 2020	On 01 March 2020, the Sponsor decided to place recruitment and dosing of subjects in the POLAR program on hold. The decision followed interactions with the French regulatory authority, ANSM and the US clinical hold of another study (POLAR-M) on 23 January 2020. As of 02 March 2020, no investigational medicinal product (IMP) was administered and no more subjects were enrolled. Enrolled subjects continued to be followed until the data cut-off date of 31 August 2020.	-

Notes:

Limitations and caveats

None reported