

**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 |
| Consent withdrawn by subject | 9 | 11 |
| Physician decision | 1 | - |
| 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 occurrences (all) | 11 / 147 (7.48%) 16 | 8 / 150 (5.33%) 10 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 32 / 147 (21.77%) 87 39 / 147 (26.53%) 61 8 / 147 (5.44%) 23 10 / 147 (6.80%) 13 | 36 / 150 (24.00%) 73 36 / 150 (24.00%) 78 7 / 150 (4.67%) 9 13 / 150 (8.67%) 18 | |
| Immune system disorders Infusion related reaction subjects affected / exposed occurrences (all) | 8 / 147 (5.44%) 9 | 2 / 150 (1.33%) 2 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) | 7 / 147 (4.76%) 7 12 / 147 (8.16%) 14 | 13 / 150 (8.67%) 14 12 / 150 (8.00%) 12 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 8 / 147 (5.44%) 8 | 3 / 150 (2.00%) 3 | |
| Investigations | | | |

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

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

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 23 / 147 (15.65%) | 18 / 150 (12.00%) | |
| occurrences (all) | 25 | 19 | |
| Palmar-plantar erythrodysesthesia 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 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • Included input from the United States Food and Drug Administration (FDA) • Updated background information |
| 12 July 2019 | <ul style="list-style-type: none"> • 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 | <ul style="list-style-type: none"> • 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 | <p>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.</p> <ul style="list-style-type: none"> • 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