Clinical trial results:
A double blinded, randomized, multi centre, Three-armed phase II trial of PledOx in two different doses in combination with FOLFOX6 compared to placebo + FOLFOX6 in patients with metastatic colorectal cancer

Summary

EudraCT number	2012-001367-76
Trial protocol	SE PT DE BG DK
Global end of trial date	12 April 2017

Results information

Result version number	v1 (current)
This version publication date	01 August 2019
First version publication date	01 August 2019
Summary attachment (see zip file)	Synopsis PLIANT CSR Part 1 (Synopsis PLIANT CSR Part 1 final 2017-11-20.pdf) Synopsis PLIANT CSR Part 2 (Synopsis PLIANT CSR Part 2 final 2017-11-17.pdf) Glimelius et al. Persistent prevention of oxaliplatin-induced. Acta Oncologica. 2018. DOI: 10.1080/0284186X.2017.1398836 (Glimelius et al. 2018a.pdf)

Trial information

Trial identification

Sponsor protocol code	PP095

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01619423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PledPharma
Sponsor organisation address	Grev Turegatan 11C, Stockholm, Sweden,
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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	12 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2016
Global end of trial reached?	Yes
Global end of trial date	12 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective Dose Escalation Phase:
To characterize the prevalence, severity, drug-relatedness and seriousness of adverse events of PledOx in two doses

Primary Objective Randomised Treatment Phase:
Assess the efficacy of two different doses of PledOx when added to FOLFOX6 chemotherapy as measured by protection from FOLFOX6 toxicity on neutropenia grade 3 or 4 (NCI-CTCAE v4)

Protection of trial subjects:

Safety Mn measurements in blood, measured at Screening, Day 13 or Day 14 of Cycle 4, End-of-Treatment and in the event of any Parkinson-like symptoms. Assessment of Mn-associated neurotoxicity (Parkinson-like symptoms) at every visit

Background therapy:

The chemotherapy was modified FOLFOX6 [25] containing oxaliplatin 85 mg/m2 during 2 h followed by calcium-levofolinate (100 mg/m2) or calcium folinate (200 mg/m2) as a 2h infusion followed by 5-FU 400 mg/m2 i.v. bolus and 5-FU continuous infusion 2400 mg/m2 during 46 h. The chemotherapy was repeated every fortnight and planned for up to eight cycles after which a break was recommended. Tumour evaluations were performed after 4 and 8 cycles. Bevacizumab (5 mg/kg) was added at the discretion of the physician.

Evidence for comparator:

Placebo. There are no effective preventive or therapeutic treatments for CIPN. Several agents have been tested, but they have so far failed. For therapy, the American Society of Clinical Oncology states that duloxetine may be used, whereas no recommendations can be given for other agents.

Actual start date of recruitment	06 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	20 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Bulgaria: 44
Country: Number of subjects enrolled	Denmark: 10

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Georgia: 33
Country: Number of subjects enrolled	Serbia: 53
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	173
EEA total number of subjects	79

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)	96
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

13 patients were randomised in part 1a (8 pts) and 1b (5 pts) and 173 patients were randomized in part 2a and 2b i.e., completed both steps of the randomization process. Thirty-nine patients were randomized in Part 2a and 134 patients were randomized in Part 2b.

Pre-assignment

Screening details:

21 pts were screened in part 1. 207 pts were screened for Part 2 (43 patients for Part 2a, 164 pts for Part 2b). 37 screening failures: 7 in part 1a+b ,4 in Part 2a and 26 in Part 2b. 4 additional pts in Part 2b completed the first step of randomization and received a randomization number, but were not allocated to treatment with IMP.

Period 1

Period 1 title	Part 2a + 2b treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Treatment in Parts 2a and 2b was blinded for the patient and investigator. To ensure blinding, the IMP was prepared by an unblinded nurse/pharmacist not otherwise involved in the study. The unblinded nurse/pharmacist prepared the IMP in a yellow-colored syringe, masking the color of the IMP. The syringe was connected to orange tubing which continued to mask the IMP also during administration. The prepared IMP, i.e. the syringe and tubing was provided to the blinded nurse who performed the admin

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 2 Group A (Pledox 2 µmol/kg)

Arm description:

PledOx 2 µmol/kg + mFOLFOX6

Arm type	Experimental
Investigational medicinal product name	PledOx 2 µmol/kg
Investigational medicinal product code	
Other name	Calmangafodipir
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

IMP (PledOx or placebo) was given as a single pre-treatment infusion over approximately 5 minutes, 10 minutes prior to oxaliplatin administration in the mFOLFOX6 regimen. The pre-treatment IMP was given before each chemotherapy cycle for up to 8 treatment cycles, every 2 weeks.

Arm title	Part 2 Group B (Pledox 5 µmol/kg)

Arm description:

Pledox 5 µmol/kg + mFOLGOX6

Arm type	Experimental
Investigational medicinal product name	PledOx 5 µmol/kg
Investigational medicinal product code	
Other name	Calmangafodipir
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

IMP (PledOx or placebo) was given as a single pre-treatment infusion over approximately 5 minutes, 10

minutes prior to oxaliplatin administration in the mFOLFOX6 regimen. The pre-treatment IMP was given before each chemotherapy cycle for up to 8 treatment cycles, every 2 weeks.

Arm title	Part 2 Group B (Pledox 10 µmol/kg)
Arm description: Pledox 10 µmol/kg + mFOLGOX6	
Arm type	Experimental
Investigational medicinal product name	Pledox 10 µmol/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: PledOx 10 µmol/kg + mFOLFOX6 in 8 cycles Name of Active ingredient: Calmangafodipir	
Arm title	Part 2 Group C (Placebo)
Arm description: Placebo + mFOLFOX6	
Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: Placebo + mFOLFOX6 in 8 cycles Name of Active ingredient: None	

Number of subjects in period 1	Part 2 Group A (Pledox 2 µmol/kg)	Part 2 Group B (Pledox 5 µmol/kg)	Part 2 Group B (Pledox 10 µmol/kg)
Started	57	45	11
Completed	44	30	6
Not completed	13	15	5
Consent withdrawn by subject	1	4	-
Physician decision	-	-	-
Adverse event, non-fatal	1	1	2
Death	1	1	1
Other reason	1	1	-
Lost to follow-up	2	2	-
Progressive disease	7	6	2

Number of subjects in period 1	Part 2 Group C (Placebo)
Started	60

Completed	48
Not completed	12
Consent withdrawn by subject	1
Physician decision	1
Adverse event, non-fatal	1
Death	-
Other reason	-
Lost to follow-up	-
Progressive disease	9

Baseline characteristics

Reporting groups	
Reporting group title	Part 2 Group A (Pledox 2 µmol/kg)
Reporting group description: PledOx 2 µmol/kg + mFOLFOX6	
Reporting group title	Part 2 Group B (Pledox 5 µmol/kg)
Reporting group description: Pledox 5 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group B (Pledox 10 µmol/kg)
Reporting group description: Pledox 10 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group C (Placebo)
Reporting group description: Placebo + mFOLFOX6	

Reporting group values	Part 2 Group A (Pledox 2 µmol/kg)	Part 2 Group B (Pledox 5 µmol/kg)	Part 2 Group B (Pledox 10 µmol/kg)
Number of subjects	57	45	11
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)	28	27	5
From 65-84 years	29	18	6
85 years and over	0	0	0
Age continuous			
Age distribution by randomised group			
Units: years			
arithmetic mean	63.1	62.6	64.8
standard deviation	± 8.9	± 10.4	± 9.4
Gender categorical Units: Subjects			
Female	16	21	6
Male	41	24	5
Race			
Frequency of subjects by race category			
Units: Subjects			
Caucasian	57	44	11
Asian or Pacific Islander		1	
African descent			
Mixed/Multi-racial			
Other			

Reporting group values	Part 2 Group C (Placebo)	Total	
Number of subjects	60	173	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	96	
From 65-84 years	24	77	
85 years and over	0	0	
Age continuous			
Age distribution by randomised group			
Units: years			
arithmetic mean	62.0		
standard deviation	± 9.4	-	
Gender categorical Units: Subjects			
Female	14	57	
Male	46	116	
Race			
Frequency of subjects by race category			
Units: Subjects			
Caucasian	58	170	
Asian or Pacific Islander	0	1	
African descent	1	1	
Mixed/Multi-racial	0	0	
Other	1	1	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who had received at least one dose of the IMP

Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

All FAS patients who had also
fulfilled the following:
o Had sufficiently complied with the CSP (i.e., had no major protocol deviations)
o Had available data for the assessment of the primary variable (i.e., at least 1 post-baseline assessment of oxaliplatin-induced neuropathy) during the treatment phase

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received at least one dose of the IMP

Reporting group values	Full Analysis Set	Per Protocol Analysis Set	Safety Analysis Set
Number of subjects	173	169	173
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)	96	94	96
From 65-84 years	77	75	77
85 years and over	0	0	0
Age continuous			
Age distribution by randomised group			
Units: years			
arithmetic mean	62.7	62.7	62.7
standard deviation	± 9.6	± 9.6	± 9.6
Gender categorical Units: Subjects			
Female	57		57
Male	116		116
Race			
Frequency of subjects by race category			
Units: Subjects			
Caucasian	170		170
Asian or Pacific Islander	1		1
African descent	1		1
Mixed/Multi-racial	0		0
Other	1		1

End points

End points reporting groups

Reporting group title	Part 2 Group A (Pledox 2 µmol/kg)
Reporting group description: PledOx 2 µmol/kg + mFOLFOX6	
Reporting group title	Part 2 Group B (Pledox 5 µmol/kg)
Reporting group description: Pledox 5 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group B (Pledox 10 µmol/kg)
Reporting group description: Pledox 10 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group C (Placebo)
Reporting group description: Placebo + mFOLFOX6	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomized patients who had received at least one dose of the IMP	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: All FAS patients who had also fulfilled the following: o Had sufficiently complied with the CSP (i.e., had no major protocol deviations) o Had available data for the assessment of the primary variable (i.e., at least 1 post-baseline assessment of oxaliplatin-induced neuropathy) during the treatment phase	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of the IMP	

Primary: Presence of neuropathy Grade 2 or higher (according to the OSSS criteria for oxaliplatin-related paresthesia/dysesthesia)

End point title	Presence of neuropathy Grade 2 or higher (according to the OSSS criteria for oxaliplatin-related paresthesia/dysesthesia)

End point description:

Presence of neuropathy Grade 2 or higher (according to the OSSS criteria for oxaliplatin-related paresthesia/dysesthesia).
Assessment of oxaliplatin-related neuropathy symptoms (neurosensory neurotoxicity) was performed prior to infusion on Day 1 of Cycle 1 and ≤36 h prior to the next cycle of each cycle in association with assessments of chemotherapy-induced AEs and DLTs and whenever any sign of neuropathy was observed. Grading was performed according to OSSS criteria for oxaliplatin-related paresthesia/dysesthesia: Grade 0=no symptoms; Grade 1= Paresthesias/dysesthesias of short duration that resolve and do not interfere with function; Grade2=Paresthesias/dysesthesias, interfering with function, but not activities of daily living. Paraesthesia, dysaesthesia persisting between cycles; Grade 3= Paresthesias/dysesthesias with pain or with functional impairment that also interfere with daily living. Paraesthesia, dysaesthesia causing functional impairment; Grade 4= Persistent parest.

End point type	Primary

End point timeframe:

This was assessed during chemotherapy treatment up to EOT.

End point values	Part 2 Group A (Pledox 2 µmol/kg)	Part 2 Group B (Pledox 5 µmol/kg)	Part 2 Group B (Pledox 10 µmol/kg)	Part 2 Group C (Placebo)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	56	45	11	60
Units: Grade 0 to 4				
CIPN	56	45	11	60

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	172			
Units: Grade 0 to 4				
CIPN	172			

Statistical analyses

Statistical analysis title	Logistic Regression Analysis for Repeated Mea

Statistical analysis description:

As originally planned in the SAP, presence of oxaliplatin-induced neuropathy of Grade 2 or higher (according to the OSSS criteria) was analyzed using a logistic regression model for repeat measures, and the GEE method was used to estimate the parameters of the model. The analysis was based on neuropathy assessments associated with the end of each of the 8 treatment cycles, and the model was adjusted for treatment group and addition of bevacizumab treatment to mFOLFOX6.

Comparison groups	Part 2 Group A (Pledox 2 µmol/kg) v Part 2 Group B (Pledox 5 µmol/kg) v Part 2 Group B (Pledox 10 µmol/kg) v Part 2 Group C (Placebo)
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1749 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.666
Confidence interval	
level	90 %
sides	1-sided
upper limit	1.163

Notes:

[1] - The type-I error rate was set to 0.10 using one-sided tests and controlled using a hierarchical structure of analyses and a closed testing procedure in the following order
1. Superiority of PledOx 2 µmol/kg and PledOx 5 µmol/kg over placebo
2. Superiority of PledOx 2 µmol/kg over placebo
3. Superiority of PledOx 5 µmol/kg over placebo
4. Superiority of PledOx 2 µmol/kg over PledOx 5 µmol/kg
5. Superiority of PledOx 2 µmol/kg, PledOx 5 µmol/kg and PledOx 10 µmol/kg over placebo.

[2] - 1. First order of the hierchical test procedure is given above
2. 0.3148
3. 0.1392
4. 0.7183

5. 0.1579

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were assessed and recorded at each hospital visit from first IMP administration to the EOT visit, 14 days after the final IMP administration. Any AEs that were ongoing at the End-of-Treatment visit were followed up until resolution or end of FU

Adverse event reporting additional description:

For each AE, site staff recorded start and stop dates, outcome, actions taken with treatment, if any other medication or treatment was given, seriousness, intensity, severity and causality.. Intensity was rated as mild, moderate, or severe. Severity was graded according to NCI-CTCAE v4 criteria as mild, moderate, severe, lifethreatening or death.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Part 2 Group A (Pledox 2 µmol/kg)
Reporting group description: PledOx 2 µmol/kg + mFOLFOX6	
Reporting group title	Part 2 Group B (Pledox 5 µmol/kg)
Reporting group description: Pledox 5 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group B (Pledox 10 µmol/kg)
Reporting group description: Pledox 10 µmol/kg + mFOLGOX6	
Reporting group title	Part 2 Group C (Placebo)
Reporting group description: Placebo + mFOLFOX6	
Reporting group title	Part 1a Pledox 2 µmol/kg
Reporting group description: -	
Reporting group title	Part 1a Pledox 10 µmol/kg
Reporting group description: -	
Reporting group title	Part 1b Pledox 2+10 µmol/kg
Reporting group description: -	
Reporting group title	Part 1b Pledox 1+5 µmol/kg
Reporting group description: -	

Serious adverse events	Part 2 Group A (Pledox 2 µmol/kg)	Part 2 Group B (Pledox 5 µmol/kg)	Part 2 Group B (Pledox 10 µmol/kg)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 57 (14.04%)	4 / 45 (8.89%)	2 / 11 (18.18%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	1	0
Injury, poisoning and procedural complications			
Brain contusion			

subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Stoma site haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Surgical and medical procedures			
Central ven			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma closure			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 11 (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
Pyrexia			
subjects affected / exposed	1 / 57 (1.75%)	1 / 45 (2.22%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 57 (1.75%)	1 / 45 (2.22%)	0 / 11 (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
Ileus			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal perforation			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Constipation			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 11 (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
Staphylococcal infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 45 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 57 (1.75%)	0 / 45 (0.00%)	0 / 11 (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
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 45 (2.22%)	0 / 11 (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

Serious adverse events	Part 2 Group C (Placebo)	Part 1a Pledox 2 µmol/kg	Part 1a Pledox 10 µmol/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 60 (10.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
number of deaths (all causes)	2	0	0
number of deaths resulting from	0	0	0

adverse events			
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Humerus fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Central ven			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Stoma closure			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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			
Chest pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Death			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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 and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Ileus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Subileus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 60 (0.00%)	1 / 5 (20.00%)	0 / 3 (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
Constipation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 5 (0.00%)	0 / 3 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1b Pledox 2+10	Part 1b Pledox 1+5	

	µmol/kg	µmol/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central ven			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma closure			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Part 2 Group A (Pledox 2 µmol/kg)	Part 2 Group B (Pledox 5 µmol/kg)	Part 2 Group B (Pledox 10 µmol/kg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 57 (96.49%)	45 / 45 (100.00%)	11 / 11 (100.00%)
Vascular disorders			
Neutropenia			
subjects affected / exposed	15 / 57 (26.32%)	17 / 45 (37.78%)	2 / 11 (18.18%)
occurrences (all)	28	44	2
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	29 / 57 (50.88%)	15 / 45 (33.33%)	5 / 11 (45.45%)
occurrences (all)	87	33	11
Peripheral sensory neuropathy			
subjects affected / exposed	15 / 57 (26.32%)	12 / 45 (26.67%)	6 / 11 (54.55%)
occurrences (all)	41	27	13
Paraesthesia			
subjects affected / exposed	11 / 57 (19.30%)	13 / 45 (28.89%)	1 / 11 (9.09%)
occurrences (all)	18	27	1
Neuropathy peripheral			
subjects affected / exposed	7 / 57 (12.28%)	11 / 45 (24.44%)	2 / 11 (18.18%)
occurrences (all)	7	17	4
Paraesthesia oral			
subjects affected / exposed	0 / 57 (0.00%)	4 / 45 (8.89%)	0 / 11 (0.00%)
occurrences (all)	0	8	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	39 / 57 (68.42%)	26 / 45 (57.78%)	5 / 11 (45.45%)
occurrences (all)	71	47	5
Anaemia			
subjects affected / exposed	13 / 57 (22.81%)	13 / 45 (28.89%)	2 / 11 (18.18%)
occurrences (all)	17	27	4

Leukopenia			
subjects affected / exposed	11 / 57 (19.30%)	12 / 45 (26.67%)	3 / 11 (27.27%)
occurrences (all)	16	27	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 57 (36.84%)	18 / 45 (40.00%)	0 / 11 (0.00%)
occurrences (all)	47	49	0
Pyrexia			
subjects affected / exposed	2 / 57 (3.51%)	8 / 45 (17.78%)	0 / 11 (0.00%)
occurrences (all)	3	11	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	20 / 57 (35.09%)	16 / 45 (35.56%)	4 / 11 (36.36%)
occurrences (all)	31	29	11
Diarrhoea			
subjects affected / exposed	17 / 57 (29.82%)	21 / 45 (46.67%)	5 / 11 (45.45%)
occurrences (all)	33	39	5
Vomiting			
subjects affected / exposed	10 / 57 (17.54%)	6 / 45 (13.33%)	1 / 11 (9.09%)
occurrences (all)	13	6	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 57 (31.58%)	11 / 45 (24.44%)	2 / 11 (18.18%)
occurrences (all)	31	12	3

Non-serious adverse events	Part 2 Group C (Placebo)	Part 1a Pledox 2 µmol/kg	Part 1a Pledox 10 µmol/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)	4 / 5 (80.00%)	3 / 3 (100.00%)
Vascular disorders			
Neutropenia			
subjects affected / exposed	29 / 60 (48.33%)	2 / 5 (40.00%)	3 / 3 (100.00%)
occurrences (all)	72	4	17
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	26 / 60 (43.33%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	81	0	0
Peripheral sensory neuropathy			

subjects affected / exposed	18 / 60 (30.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	59	0	0
Paraesthesia			
subjects affected / exposed	12 / 60 (20.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	21	0	0
Neuropathy peripheral			
subjects affected / exposed	9 / 60 (15.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	19	0	0
Paraesthesia oral			
subjects affected / exposed	6 / 60 (10.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	8	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	38 / 60 (63.33%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	75	0	0
Anaemia			
subjects affected / exposed	16 / 60 (26.67%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	24	0	0
Leukopenia			
subjects affected / exposed	22 / 60 (36.67%)	2 / 5 (40.00%)	3 / 3 (100.00%)
occurrences (all)	51	7	19
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 60 (51.67%)	1 / 5 (20.00%)	1 / 3 (33.33%)
occurrences (all)	91	2	2
Pyrexia			
subjects affected / exposed	9 / 60 (15.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	13	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	28 / 60 (46.67%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	76	0	0
Diarrhoea			
subjects affected / exposed	20 / 60 (33.33%)	1 / 5 (20.00%)	3 / 3 (100.00%)
occurrences (all)	46	1	5
Vomiting			

subjects affected / exposed	9 / 60 (15.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	18	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 60 (26.67%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences (all)	35	0	0

Non-serious adverse events	Part 1b Pledox 2+10 µmol/kg	Part 1b Pledox 1+5 µmol/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	
Vascular disorders			
Neutropenia			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	8	12	
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Paraesthesia oral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	

Leukopenia			
subjects affected / exposed	2 / 2 (100.00%)	2 / 3 (66.67%)	
occurrences (all)	15	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	3 / 3 (100.00%)	
occurrences (all)	1	3	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2013	Changed dose from 10 to 5 µmol/kg for the highest dose group.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported