Clinical trial results:
A Randomised Open Label Exploratory, Safety and Tolerability Study with PP100-01 in Patients Treated with the 12-hour Regimen of N-Acetylcysteine for Paracetamol/Acetaminophen Overdose

Summary

EudraCT number	2017-000246-21
Trial protocol	GB
Global end of trial date	08 August 2018

Results information

Result version number	v1 (current)
This version publication date	06 September 2019
First version publication date	06 September 2019

Trial information

Trial identification

Sponsor protocol code	PP100-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03177395
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PledPharma
Sponsor organisation address	Grev Turegatan 10C, Stockholm, Sweden, 11446
Public contact	Malin Nittve, PledPharma AB, +46 (0)708368702, malin.nittve@pledpharma.se
Scientific contact	Malin Nittve, PledPharma AB, +46 (0)708368702, malin.nittve@pledpharma.se

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	03 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2018
Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Paracetamol can be harmful to the liver when an excessive dose has been taken. To help prevent liver damage, an antidote known as acetylcysteine is given. However a few patients can develop liver damage even if they get acetylcysteine. This study will give a new drug (calmangafodipir - PP100-01) in combination with a new 12-hour regimen for giving acetylcysteine. The principal research question is does the combination of calmangafodipir and acetylcysteine produce any unexpected side-effects?

Protection of trial subjects:

The participants were given an oral explanation and a written Patient Information Sheet (PIS) explaining the aims of the study and the potential risks and benefits of the study treatments. The participant was given enough time to consider the study and ask questions regarding their participation in the study. Both the participant and the person delegated to take consent, signed and personally dated the ICF. Only patients with capacity were invited to participate in the study. Potential entry into the study depended on the patient's blood results confirming need for NAC and an assessment of capacity by a doctor in the Emergency Department. . All patients requiring NAC treatment were given this regardless of entry into the study.

Background therapy:

To address the high incidence of ADRs and prolonged duration of the standard NAC regimen, a shorter 12 h intravenous regimen has been developed
(the 'SNAP' regimen). The NAC regimen was 300 mg/kg NAC IV (200 mg/ml) in 5% glucose (dextrose) or 0.9% sodium chloride over 12 hours. This was divided as follows:
• 100mg/kg of NAC in 200 mL over 2 hours ("loading dose"), then
• 200 mg/kg of NAC in 1000 ml over l0 hours.
Dose of NAC was adjusted according to participant weight

Evidence for comparator:

Acetylcysteine (NAC) is effective at preventing liver injury if administered promptly, but it is substantially less effective if started later than around 8 h after overdose.

Actual start date of recruitment	05 June 2017
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	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	23
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

To meet the target of 24 participants randomised, a total of 304 patients were screened and assessed for eligibility. Patients screened had toxicology presentations that included but were not exclusively paracetamol overdose. The main reasons for not being included was failure to meet inclusion criteria (n=216) or due to exclusion criteria (n=39).

Pre-assignment

Screening details:

Decision to treat with NAC is based on a nomogram to identify patients who require NAC treatment following a paracetamol overdose . This is based on paracetamol concentration and time from ingestion. In patients presenting later than 8h as well as staggered POD, NAC treatment is initiated if the patient had ingested more than 150 mg/kg APAP

Pre-assignment period milestones

Number of subjects started	24
Number of subjects completed	24

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Allocation sequence for each dosing cohort was created by an Edinburgh Clinical Trials Unit (ECTU) programmer using computer-generated randomnumbers, using blocking to ensure the required 6:2 ratio. The randomisation list was held centrally at ECTU in order to conceal treatment allocations until these were implemented via the secureweb-based randomisation system. No blinding of participants or emergency department staff. Statistical analysis plan was written blinded to treatment allocations

Arms

Are arms mutually exclusive?	Yes
Arm title	NAC alone

Arm description:

NAC infusion 100mg/kg in 200ml 'loading dose' at timepoint '0'. 12 hour NAC regime will be continued with the second dose: 200mg/kg NAC in 1000ml i.v. over 10hr as per standard care protocol in NHS Lothian. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml i.v administered over a further 10 hours if any of the following criteria were reached:
• the ALT has more than doubled since the admission measurement, OR
• the ALT is two times the upper limit of normal or more (≥100 IU/L), OR
• the INR is greater than 1.3, OR
• paracetamol concentration > 20 mg/mL

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC

Arm description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
Group A: PP100-01 (2 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Arm type	Experimental

Investigational medicinal product name	Calmangafodipir
Investigational medicinal product code	PP100-01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Treatment started with the first NAC bag of 100 mg/kg in 200 ml (“loading dose”) at time point ‘0’. PP100-01 treatment (2 µmol/kg, 5 µmol/kg or 10 µmol/kg) was administered intravenously as a bolus infusion over 5 minutes at the dose specified by the dosing cohort following the loading dose of NAC. The 12-hour NAC regimen was continued with the second dose: 200 mg/kg NAC in 1000 mL i.v over 10 hours. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml i.v administered over a further 10 hours if any of the following criteria were reached:
• the ALT has more than doubled since the admission measurement, OR
• the ALT is two times the upper limit of normal or more (≥100 IU/L), OR
• the INR is greater than 1.3, OR
• paracetamol concentration > 20 mg/mL

Arm title	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC

Arm description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (5 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Arm type	Experimental
Investigational medicinal product name	Calmangafodipir
Investigational medicinal product code	PP100-01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Treatment started with the first NAC bag of 100 mg/kg in 200 ml (“loading dose”) at time point ‘0’. PP100-01 treatment (2 µmol/kg, 5 µmol/kg or 10 µmol/kg) was administered intravenously as a bolus infusion over 5 minutes at the dose specified by the dosing cohort following the loading dose of NAC. The 12-hour NAC regimen was continued with the second dose: 200 mg/kg NAC in 1000 mL i.v over 10 hours. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml i.v administered over a further 10 hours if any of the following criteria were reached:
• the ALT has more than doubled since the admission measurement, OR
• the ALT is two times the upper limit of normal or more (≥100 IU/L), OR
• the INR is greater than 1.3, OR
• paracetamol concentration > 20 mg/mL

Arm title	Group C: PP001-01 (Calmangafodipir) + NAC

Arm description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (10 umol/kg calmangafodipir) after the "loading" dose of NAC
PP100-01 treatment is administered intravenously over 5 minutes.

Arm type	Experimental
Investigational medicinal product name	Calmangafodipir
Investigational medicinal product code	PP100-01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Treatment started with the first NAC bag of 100 mg/kg in 200 ml (“loading dose”) at time point ‘0’. PP100-01 treatment (2 µmol/kg, 5 µmol/kg or 10 µmol/kg) was administered intravenously as a bolus infusion over 5 minutes at the dose specified by the dosing cohort following the loading dose of NAC. The 12-hour NAC regimen was continued with the second dose: 200 mg/kg NAC in 1000 mL i.v over 10 hours. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml

i.v administered over a further 10 hours if any of the following criteria were reached:
• the ALT has more than doubled since the admission measurement, OR
• the ALT is two times the upper limit of normal or more (≥100 IU/L), OR
• the INR is greater than 1.3, OR
• paracetamol concentration > 20 mg/mL

Number of subjects in period 1	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC
Started	6	6	6
Completed	6	6	6

Number of subjects in period 1	Group C: PP001-01 (Calmangafodipir) + NAC
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	NAC alone
Reporting group description:	
NAC infusion 100mg/kg in 200ml 'loading dose' at timepoint '0'. 12 hour NAC regime will be continued with the second dose: 200mg/kg NAC in 1000ml i.v. over 10hr as per standard care protocol in NHS Lothian. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml i.v administered over a further 10 hours if any of the following criteria were reached: • the ALT has more than doubled since the admission measurement, OR • the ALT is two times the upper limit of normal or more (≥100 IU/L), OR • the INR is greater than 1.3, OR • paracetamol concentration > 20 mg/mL	
Reporting group title	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC
Reporting group description:	
In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive: Group A: PP100-01 (2 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.	
Reporting group title	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC
Reporting group description:	
In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive: PP100-01 (5 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.	
Reporting group title	Group C: PP001-01 (Calmangafodipir) + NAC
Reporting group description:	
In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive: PP100-01 (10 umol/kg calmangafodipir) after the "loading" dose of NAC PP100-01 treatment is administered intravenously over 5 minutes.	

Reporting group values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC
Number of subjects	6	6	6
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)	6	5	6
From 65-84 years	0	1	0
85 years and over	0	0	0
Gender categorical			
All treatment groups included both male and female patients with an overall balance of 13 female versus 11 male patients			
Units: Subjects			
Female	2	4	4

Male	4	2	2

Type of overdose			
Type of overdose			
Units: Subjects			
Acute, ≤8 h to NAC	2	4	4
Acute, over 8 h to NAC	3	2	2
Staggered intentional	0	0	0
Supra-therapeutic	1	0	0
Any other drugs ingested			
Any other drugs ingested			
Units: Subjects			
yes	5	4	5
No	1	2	1
Time from ingestion of paracetamol to hospital presentation (hours)			
Time from ingestion of paracetamol to hospital presentation (hours)			
Units: hours			
arithmetic mean	8.8	6.0	5.8
standard deviation	± 6.2	± 2.6	± 2.1
Presentation paracetamol concentration (mg/L)			
Presentation paracetamol concentration (mg/L)			
Units: mg/mL			
arithmetic mean	76	127	74
standard deviation	± 81	± 90	± 44
Total paracetamol ingested (mg/kg)			
Total paracetamol ingested (mg/kg)			
Units: mg/kg			
arithmetic mean	185	235	229
standard deviation	± 156	± 77	± 72
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Units: hours			
arithmetic mean	12.1	9.8	10.2
standard deviation	± 5.2	± 6.5	± 6.9
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Units: hours			
arithmetic mean	NA	12.6	10.8
standard deviation	±	± 6.8	± 4.1
Serum creatinine (µmol/L)			
Serum creatinine (µmol/L)			
Units: µmol/L			
arithmetic mean	74.7	67.5	67.3
standard deviation	± 11.0	± 13.3	± 17.2

Reporting group values	Group C: PP001-01 (Calmangafodipir) + NAC	Total	
Number of subjects	6	24	

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)	6	23	
From 65-84 years	0	1	
85 years and over	0	0	
Gender categorical			
All treatment groups included both male and female patients with an overall balance of 13 female versus 11 male patients			
Units: Subjects			
Female	3	13	
Male	3	11	
Type of overdose			
Type of overdose			
Units: Subjects			
Acute, ≤8 h to NAC	4	14	
Acute, over 8 h to NAC	1	8	
Staggered intentional	1	1	
Supra-therapeutic	0	1	
Any other drugs ingested			
Any other drugs ingested			
Units: Subjects			
yes	5	19	
No	1	5	
Time from ingestion of paracetamol to hospital presentation (hours)			
Time from ingestion of paracetamol to hospital presentation (hours)			
Units: hours arithmetic mean standard deviation	 4.9 ± 2.1	 -	
Presentation paracetamol concentration (mg/L)			
Presentation paracetamol concentration (mg/L)			
Units: mg/mL arithmetic mean standard deviation	 127 ± 47	 -	
Total paracetamol ingested (mg/kg)			
Total paracetamol ingested (mg/kg)			
Units: mg/kg arithmetic mean standard deviation	 397 ± 476	 -	
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Units: hours arithmetic mean	 8.6		

standard deviation	± 4.1	-	
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Units: hours			
arithmetic mean	11.8		
standard deviation	± 5.4	-	
Serum creatinine (µmol/L)			
Serum creatinine (µmol/L)			
Units: µmol/L			
arithmetic mean	69.5		
standard deviation	± 13.1	-	

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Patients will be included in the full analysis population, the primary population for analysis of efficacy, if they have received any PP100–01 or NAC. Data will be analysed according to the randomised treatment group. The stringent per-protocol population includes patients from the full analysis population for whom the study protocol has been followed without any major violations. The population for safety analysis will be patients who have
received any PP100–01 or NAC. Data will be analysed according to the treatment received (NAC plus PP100– 01, or NAC alone)

Reporting group values	Full analysis		
Number of subjects	24		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	23		
From 65-84 years	1		
85 years and over	0		
Gender categorical			
All treatment groups included both male and female patients with an overall balance of 13 female versus 11 male patients			
Units: Subjects			
Female	13		
Male	11		
Type of overdose			
Type of overdose			
Units: Subjects			
Acute, ≤8 h to NAC	14		
Acute, over 8 h to NAC	8		
Staggered intentional	1		
Supra-therapeutic	1		

Any other drugs ingested			
Any other drugs ingested			
Units: Subjects			
yes	19		
No	5		
Time from ingestion of paracetamol to hospital presentation (hours)			
Time from ingestion of paracetamol to hospital presentation (hours)			
Units: hours			
arithmetic mean	6.4		
standard deviation	± 6.2		
Presentation paracetamol concentration (mg/L)			
Presentation paracetamol concentration (mg/L)			
Units: mg/mL			
arithmetic mean	101		
standard deviation	± 66		
Total paracetamol ingested (mg/kg)			
Total paracetamol ingested (mg/kg)			
Units: mg/kg			
arithmetic mean	262		
standard deviation	± 195		
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Time from ingestion of paracetamol to start of NAC treatment (hours)			
Units: hours			
arithmetic mean	10.2		
standard deviation	± 5.7		
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Time from ingestion of paracetamol to start of calmangafodipir (hours)			
Units: hours			
arithmetic mean	11.7		
standard deviation	± 5.4		
Serum creatinine (µmol/L)			
Serum creatinine (µmol/L)			
Units: µmol/L			
arithmetic mean	69.8		
standard deviation	± 13.6		

End points

End points reporting groups

Reporting group title	NAC alone

Reporting group description:

NAC infusion 100mg/kg in 200ml 'loading dose' at timepoint '0'. 12 hour NAC regime will be continued with the second dose: 200mg/kg NAC in 1000ml i.v. over 10hr as per standard care protocol in NHS Lothian. At the end of the 12-hour NAC regimen the decision to continue NAC was made by assessment of the clinical blood sample taken at the 10-hour time-point. NAC was continued at 200 mg/kg in 1000 ml i.v administered over a further 10 hours if any of the following criteria were reached:
• the ALT has more than doubled since the admission measurement, OR
• the ALT is two times the upper limit of normal or more (≥100 IU/L), OR
• the INR is greater than 1.3, OR
• paracetamol concentration > 20 mg/mL

Reporting group title	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
Group A: PP100-01 (2 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Reporting group title	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (5 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Reporting group title	Group C: PP001-01 (Calmangafodipir) + NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (10 umol/kg calmangafodipir) after the "loading" dose of NAC
PP100-01 treatment is administered intravenously over 5 minutes.

Subject analysis set title	Full analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Patients will be included in the full analysis population, the primary population for analysis of efficacy, if they have received any PP100–01 or NAC. Data will be analysed according to the randomised treatment group. The stringent per-protocol population includes patients from the full analysis population for whom the study protocol has been followed without any major violations. The population for safety analysis will be patients who have
received any PP100–01 or NAC. Data will be analysed according to the treatment received (NAC plus PP100– 01, or NAC alone)

Primary: Safety Events

End point title	Safety Events[1]

End point description:

All randomised patientswere analysed for the safety and tolerability primary outcomes. During the 7 days after randomisation 23 out of 24 patients had at least one AE. Eleven patients had at least one SAE within the 90 day follow up period; 5 patients had at least one SAE within 7 days of randomisation. These SAEs were spread across the 4 treatment groups.

The primary objective of this phase 1 trial was to assess the adverse events (AEs) and serious adverse events (SAEs) associated with calmangafodipir co-treatment with the SNAP NAC treatment regime in patients with paracetamol overdose. The data generated were descriptive; there was no hypothesis tested. Therefore, we did not perform any analysis which would generate a P value

End point type	Primary

End point timeframe:

90 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective of this phase 1 trial was to assess the adverse events (AEs) and serious adverse events (SAEs) associated with calmangafodipir co-treatment with the SNAP NAC treatment regime in patients with paracetamol overdose. The data generated were descriptive; there was no hypothesis tested. Therefore, we did not perform any analysis which would generate a P value

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: subjects				
Any AE	6	6	6	6
Any SAE	2	4	2	3
AE after commencement of NAC treatment	6	5	6	6
SAE after commencement of NAC treatment	1	1	1	2
AE where outcome was death	0	0	1	0
AE unrelated to NAC	3	5	3	5
AE possibly related to NAC	2	2	2	2
AE probably related to NAC	3	2	3	2
AE definitely related to NAC	2	3	1	1
AE unrelated to PP100-01	6	6	5	6
AE possibly related to PP001-01	0	4	2	2
Ae probably related to PP100-01	0	0	0	0
AE definitely related to PP100-01	0	0	0	0
Any SUSAR	0	0	0	1
Any SUSAR related to NAC	0	0	0	0
SUSAR to PP100-01	0	0	0	1
SUSAR to NAC and PP100-01	0	0	0	0

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: subjects				
Any AE	24			
Any SAE	11			
AE after commencement of NAC treatment	23			
SAE after commencement of NAC treatment	5			
AE where outcome was death	1			
AE unrelated to NAC	16			
AE possibly related to NAC	8			
AE probably related to NAC	10			
AE definitely related to NAC	7			
AE unrelated to PP100-01	23			
AE possibly related to PP001-01	8			

Ae probably related to PP100-01	0			
AE definitely related to PP100-01	0			
Any SUSAR	1			
Any SUSAR related to NAC	0			
SUSAR to PP100-01	1			
SUSAR to NAC and PP100-01	0			

Statistical analyses

No statistical analyses for this end point

Secondary: ALT

End point title	ALT

End point description:

ALT was summarised descriptively by treatment group and overall at baseline, 10 h and 20 h. Change from baseline was also summarised.

End point type	Secondary

End point timeframe:

Baseline, 10 and 20 hours after

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: U/L				
geometric mean (standard deviation)				
Baseline	42.5 (± 3.6)	24.6 (± 2.1)	29.4 (± 2.3)	17.7 (± 1.5)
10 hours	41.4 (± 3.3)	22.9 (± 1.8)	25.3 (± 2.1)	15.0 (± 1.3)
20 hours	43.3 (± 3.8)	20.4 (± 1.9)	25.4 (± 1.8)	16.4 (± 1.5)
Change from baseline	1.02 (± 1.62)	0.83 (± 1.25)	0.87 (± 1.34)	0.92 (± 1.58)

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: U/L				
geometric mean (standard deviation)				
Baseline	27.2 (± 2.4)			
10 hours	24.5 (± 2.2)			
20 hours	24.6 (± 2.3)			
Change from baseline	0.91 (± 1.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: INR

End point title	INR

End point description:

Relative change from baseline to 20 h - ratio was also assessed

End point type	Secondary

End point timeframe:

Baseline, 10 and 20 hours and Relative change from baseline to 20 h - ratio

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: NA				
arithmetic mean (standard deviation)				
Baseline	1.02 (± 0.04)	1.00 (± 0.12)	0.98 (± 0.04)	1.05 (± 0.14)
10 hours	1.30 (± 0.18)	1.17 (± 0.20)	1.20 (± 0.00)	1.22 (± 0.25)
20 hours	1.18 (± 0.21)	1.07 (± 0.19)	1.08 (± 0.04)	1.17 (± 0.23)
Relative change from baseline to 20 h - ratio	1.15 (± 1.17)	1.07 (± 1.12)	1.10 (± 1.07)	1.10 (± 1.10)

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: NA				
arithmetic mean (standard deviation)				
Baseline	1.01 (± 0.09)			
10 hours	1.22 (± 0.18)			
20 hours	1.13 (± 0.18)			
Relative change from baseline to 20 h - ratio	1.11 (± 1.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of additional NAC infusions after 12 h regimen

End point title	Number of additional NAC infusions after 12 h regimen

End point description:

End point type	Secondary

End point timeframe:

After 12 hours NAC regimen

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: subjects				
None	3	5	6	5
One	1	1	0	1
Two	2	0	0	0

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: subjects				
None	19			
One	3			
Two	2			

Statistical analyses

No statistical analyses for this end point

Secondary: K18

End point title	K18

End point description:

Relative change from baseline to 20 h – ratio was also assessed

End point type	Secondary

End point timeframe:

Baseline, 10 hours and 20 hours

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: U/L				
geometric mean (standard deviation)				
Baseline (2 h)	187 (± 2.20)	177 (± 1.82)	193 (± 1.56)	128 (± 1.25)
10h	182 (± 1.95)	152 (± 1.56)	170 (± 1.42)	111 (± 1.18)
20h	347 (± 3.18)	229 (± 1.94)	172 (± 1.45)	181 (± 1.73)
Relative change from baseline to 20 h – ratio	1.85 (± 1.47)	1.29 (± 1.89)	0.89 (± 1.57)	1.41 (± 1.83)

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: U/L				
geometric mean (standard deviation)				
Baseline (2 h)	169 (± 1.72)			
10h	151 (± 1.58)			
20h	223 (± 2.12)			
Relative change from baseline to 20 h – ratio	1.32 (± 1.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: ccK18

End point title	ccK18
End point description:	
Relative change from baseline to 20 h - ratio	
End point type	Secondary
End point timeframe:	
At Baseline, 10 hours and 20 hours	

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: U/L				
geometric mean (standard deviation)				
Baseline (2 h)	67 (± 1.99)	45 (± 1.33)	84 (± 1.80)	104 (± 2.44)
10h	72 (± 2.24)	53 (± 1.25)	56 (± 1.57)	78 (± 2.12)
20h	149 (± 3.34)	66 (± 1.34)	85 (± 1.62)	111 (± 2.56)
Relative change from baseline to 20 h - ratio	2.22 (± 1.77)	1.49 (± 1.55)	1.02 (± 1.79)	1.08 (± 2.44)

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: U/L				
geometric mean (standard deviation)				
Baseline (2 h)	71 (± 1.99)			
10h	64 (± 1.80)			
20h	98 (± 2.27)			
Relative change from baseline to 20 h - ratio	1.38 (± 1.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: miR-122 (DCt)

End point title	miR-122 (DCt)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 10 hours and 20 hours

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: DCt				

arithmetic mean (standard deviation)				
Baseline (2 h)	5.58 (± 3.36)	5.85 (± 1.50)	4.43 (± 3.92)	8.73 (± 2.36)
10h	5.41 (± 3.86)	6.14 (± 1.99)	5.01 (± 3.36)	9.00 (± 1.45)
20h	4.85 (± 3.97)	7.12 (± 2.26)	4.49 (± 2.93)	8.44 (± 1.50)

End point values	Full analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	24			
Units: DCt				
arithmetic mean (standard deviation)				
Baseline (2 h)	6.15 (± 3.18)			
10h	6.39 (± 3.09)			
20h	6.22 (± 3.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: miR-122 (copies/mcL)

End point title	miR-122 (copies/mcL)
End point description:	
Relative change from baseline to 20 h - ratio was also assessed	
End point type	Secondary
End point timeframe:	
Baseline, 10 hours and 20 hours	

End point values	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC	Group C: PP001-01 (Calmangafodipir) + NAC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: copies/mcL				
geometric mean (standard deviation)				
Baseline (2h)	146363 (± 11.7)	116749 (± 2.4)	194075 (± 13.5)	36051 (± 3.9)
10h	206205 (± 13.0)	109882 (± 3.3)	196732 (± 9.4)	37066 (± 2.2)
20 h	216256 (± 10.8)	57664 (± 3.8)	202271 (± 7.7)	40745 (± 3.2)
Relative change from baseline to 20 h - ratio	1.48 (± 5.71)	0.49 (± 1.98)	1.04 (± 8.28)	1.13 (± 2.96)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were collected 7, 30 and 90 days after randomisation

Adverse event reporting additional description:

As were events of special interest: representation to hospital (any reason), representation with liver injury, repeat overdose, death and transfer to liver transplantation unit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	NAC alone

Reporting group description:

NAC infusion 100mg/kg in 200ml 'loading dose' at timepoint '0'. 12 hour NAC regime will be continued with the second dose: 200mg/kg NAC in 1000ml i.v. over 10hr as per standard care protocol in NHS Lothian.

Reporting group title	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
Group A: PP100-01 (2 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Reporting group title	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (5 umol/kg calmangafodipir) after the "loading" dose of NAC. PP100-01 treatment is administered intravenously over 5 minutes.

Reporting group title	Group C: PP001-01 (Calmangafodipir) + NAC

Reporting group description:

In addition to the standard care NAC regime, participants will be allocated into a dosing cohort to receive:
PP100-01 (10 umol/kg calmangafodipir) after the "loading" dose of NAC
PP100-01 treatment is administered intravenously over 5 minutes.

Serious adverse events	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	4 / 6 (66.67%)	4 / 6 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: There were 9 repeat overdoses for 4 participants, with one subject (11019 (NAC + 10 µmol/kg PP100-01)) presenting to hospital with 5 separate overdoses		

subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Cardiac disorders			
cardiac disorders	Additional description: Adverse event of 'Death - caused by bronchopneumonia (possible aspiration) and ischaemic heart disease' experienced by participant 11015 (NAC+5 µmol/kg PP100-01)		
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
gastrointestinal disorders			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders	Additional description: 3 participants recorded SAEs relating to psychiatric disorders (depressive episode (11018 (NAC alone)), mental health crisis (11005 (NAC + 2 µmol/kg PP100-01)), mental health issue (11006 NAC + 2 µmol/kg PP100-01))		
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (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
Infections and infestations			
Infections and infestations	Additional description: Adverse event of 'Death - caused by bronchopneumonia (possible aspiration) and ischaemic heart disease' experienced by participant 11015 (NAC+5 µmol/kg PP100-01)		
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	Group C: PP001-01 (Calmangafodipir) + NAC		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: There were 9 repeat overdoses for 4 participants, with one subject (11019 (NAC + 10 µmol/kg PP100-01)) presenting to hospital with 5 separate overdoses		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
cardiac disorders	Additional description: Adverse event of 'Death - caused by bronchopneumonia (possible aspiration) and ischaemic heart disease' experienced by participant 11015 (NAC+5 µmol/kg PP100-01)		
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
gastrointestinal disorders			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychiatric disorders	Additional description: 3 participants recorded SAEs relating to psychiatric disorders (depressive episode (11018 (NAC alone)), mental health crisis (11005 (NAC + 2 µmol/kg PP100-01)), mental health issue (11006 NAC + 2 µmol/kg PP100-01))		

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations	Additional description: Adverse event of 'Death - caused by bronchopneumonia (possible aspiration) and ischaemic heart disease' experienced by participant 11015 (NAC+5 µmol/kg PP100-01)		
subjects affected / exposed	2 / 6 (33.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	NAC alone	Group A: PP100-01 (2 umol/kg calmangafodipir) +NAC	Group B: PP100-01 (Calmangafodipir) 5 umol/kg + NAC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Vascular disorders			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Injury, poisoning and procedural complications			

Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Cardiac disorders			
Cardiac disorderd			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	1	3	2
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	5 / 6 (83.33%)	6 / 6 (100.00%)	4 / 6 (66.67%)
occurrences (all)	5	6	4
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infections and infestations			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

Non-serious adverse events	Group C: PP001-01		

	(Calmangafodipir) + NAC		
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	 3 / 6 (50.00%) 3		
Cardiac disorders Cardiac disorderd subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	 5 / 6 (83.33%) 5		
Skin and subcutaneous tissue disorders			

Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3		
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2017	There was one substantial amendment to the protocol after study start to provide clarification around timing of assessments and ensure alignment of the protocol with relevant SOPs and instructions. The protocol and PIS-ICF were updated accordingly and this amendment were approved and implemented on 10th August 2017

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No pts developed hepatotoxicity (ALT over 1000 U/L) or ALF. Pts not stratified at randomisation by risk of developing hepatoxicity or ALF. Small pts No per group should be considered when interpreting the effect of calmangafodipir

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30621764

http://www.ncbi.nlm.nih.gov/pubmed/31311721