Clinical trial results:
A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE IV CLINICAL STUDY OF THE EFFICACY AND SAFETY OF A NEW FORMULATION OF PARACETAMOL FOR THE MANAGEMENT OF FEVER OF INFECTIOUS ORIGIN

Summary

EudraCT number	2014-002588-14
Trial protocol	GR
Global end of trial date	19 March 2016

Results information

Result version number	v1 (current)
This version publication date	26 November 2021
First version publication date	26 November 2021
Summary attachment (see zip file)	Giamarellos2017 (FINAL PUBLICATION.pdf)

Trial information

Trial identification

Sponsor protocol code	APOTEL-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02283203
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA
Sponsor organisation address	14th Km National Road 1, Kifissia, Greece, 14564
Public contact	Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA, 30 2108072512, unipharma@uni-pharma.gr
Scientific contact	Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories SA, 30 2108072512, unipharma@uni-pharma.gr

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 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2016
Global end of trial reached?	Yes
Global end of trial date	19 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A new formulation of paracetamol for intravenous administration has been manufactured in Greece by the industry Uni-Pharma (APOTEL Max®). According to this new formulation, 1g of paracetamol is provided as a flask diluted into 100ml volume with the possibility of immediate connection with the infusion device of the patient. This formulation provides the advantage of a dilution ready-to-use which equals considerable financial benefit; nursing staff is not pre-occupied with the preparation of dilutions and the amount of consumables required for the preparation of this dilution is significantly decreased. Taking into consideration that the antipyretic effect of intravenous paracetamol has never been studied compared with other agents in patients and available data come from studies in volunteers with experimental endotoxemia, the present study compares the efficacy of the new APOTEL Max® formulation versus placebo for the management of fever of infectious origin.

Protection of trial subjects:

Administration of 1 g paracetamol as rescue medication (APOTEL MAX) 3 h after the start of the study drug infusion on patient demand or at the discretion of the attending physician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 80
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	65
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on February 18th 2015 and the last on March 19th 2016, in 5 centers in Greece. In total, 39 patients were randomized to the placebo arm and 41 to the paracetamol arm.

Pre-assignment

Screening details:

In total, 231 patients were asked to provide written consent for assessment of eligibility, and 185 provided this. As intense follow-up of enrolled patients was mandated as per the protocol, once a patient had been enrolled, no screening was run in parallel, to avoid mistakes by the study personnel during follow-up.

Period 1

Period 1 title	First visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The study drugs (placebo or active drug) were constructed by the sponsor to be visually similar. A separate allocation sequence was designed for each study site by an independent statistician, who was the only holder of the allocation sequence.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental
Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device

that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 1	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 2	
Period 2 title	Second visit-0.5h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 2	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 3

Period 3 title	Third visit-1h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 3	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 4

Period 4 title	Fourth visit-2h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 4	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 5

Period 5 title	Fifth visit-3h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 5	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 6

Period 6 title	Sixth visit-4h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 6	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 7

Period 7 title	Seventh visit-5h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 7	Placebo group	Active drug group
Started	39	41
Completed	39	41

Period 8

Period 8 title	Eighth visit-6h postinfusion
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo group

Arm description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Arm title	Active drug group

Arm description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Arm type	Experimental

Investigational medicinal product name	Apotel max
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Polypropylene bag with a final volume of 100 ml, which was connected directly to the infusion device that led to a catheter already cannulated in one antecubital vein. Infused within 15 min.

Number of subjects in period 8	Placebo group	Active drug group
Started	39	41
Completed	39	41

Baseline characteristics

Reporting groups	
Reporting group title	Placebo group
Reporting group description:	
Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.	
Reporting group title	Active drug group
Reporting group description:	
Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.	

Reporting group values	Placebo group	Active drug group	Total
Number of subjects	39	41	80
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	50.1	53.0	
standard deviation	± 24.7	± 20.8	-
Gender categorical			
Units: Subjects			
Female	21	21	42
Male	18	20	38

End points

End points reporting groups

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Placebo group

Reporting group description:

Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Reporting group title	Active drug group

Reporting group description:

Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.

Primary: Achievement of defervescence

End point title	Achievement of defervescence[1]

End point description:

Percentage of patients found with sustained defervescence during the 6-h follow-up. Achievement of defervescence was defined as any core body temperature ≤37.1°C.

End point type	Primary

End point timeframe:

6 h after administration

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: Comparisons of the advent of defervescence and of the need for rescue medication between the groups were carried out using the Fisher exact test

End point values	Placebo group	Active drug group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percent				
number (not applicable)	38.5	80.5		

Statistical analyses

No statistical analyses for this end point

Primary: Time to defervescence

End point title	Time to defervescence[2]

End point description:

Median time to defervescence

End point type	Primary

End point timeframe:

6 hours after administration

Notes:

[2] - 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 median and interquartile ranges of time to the advent of defervescence and to the need for rescue medication were measured after Kaplan–Meier analysis

End point values	Placebo group	Active drug group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: hour				
median (inter-quartile range (Q1-Q3))	6 (3 to 6)	3 (1 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue medication

End point title	Rescue medication

End point description:

Need for administration of rescue medication

End point type	Secondary

End point timeframe:

6 hours after administration

End point values	Placebo group	Active drug group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percent				
number (not applicable)	38.5	12.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
10 days after administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Placebo group
Reporting group description:	
Patients were randomly assigned to the placebo group, receiving excipients diluted in water for injection at a volume of 100 ml and infused within 15 min. The specific excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.	
Reporting group title	Active drug group
Reporting group description:	
Patients were randomly assigned to active drug group receiving 1 g paracetamol (Apotel max, Uni-Pharma SA) diluted in water for injection at a volume of 100ml and infused within 15 min. The inactive excipients were hydroxypropylbetadex, monothioglycerol, disodium edetate, sodium chloride and disodium phosphate dihydrate.	

Serious adverse events	Placebo group	Active drug group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
General disorders and administration site conditions			
Death	Additional description: Deaths, which occurred more than 24 h after infusion of the study drug; in all cases, this was caused by the underlying infection.		
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	Placebo group	Active drug group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	2 / 41 (4.88%)	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 41 (2.44%) 1	
Endocrine disorders Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 41 (2.44%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27792836