Clinical trial results:
A randomised, blinded, placebo-controlled Phase 2a study to evaluate the safety and efficacy of Artesunate treatment in severely injured trauma patients with traumatic haemorrhage.

Summary

EudraCT number	2015-000301-40
Trial protocol	GB
Global end of trial date	10 August 2019

Results information

Result version number	v1 (current)
This version publication date	16 December 2020
First version publication date	16 December 2020

Trial information

Trial identification

Sponsor protocol code	009531

Additional study identifiers

ISRCTN number	ISRCTN15731357
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary, University of London
Sponsor organisation address	QM Innovation building, 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Clinical Trials Coordinator, Trauma Sciences, Blizard Institute, Queen Mary University London, 44 02035940728, lourdes.anton@nhs.net
Scientific contact	Clinical Trials Coordinator, Trauma Sciences, Blizard Institute, Queen Mary University London, 44 02035940728, lourdes.anton@nhs.net

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	17 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 May 2019
Global end of trial reached?	Yes
Global end of trial date	10 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether Artesunate is safe and effective in treating severely-injured patients with traumatic haemorrhage in addition to the current standard management.

Protection of trial subjects:

Informed Consent
Detailed consideration to the informed consent process was undertaken, to ensure that subjects rights to informed consent were protected, whilst minimising distress to the subject and his/her relatives/next of kin. The Mental Capacity Act (England; 2005) and Declaration of Helsinki (World Medical Association; 2013) were used for guidance in the case of incapacitated subjects.

Safety
The study underwent periodic review by an independent Data Monitoring Comittee (DMC) and a planned formal analysis of safety data was performed at the interim review (after 56 patients were recruited). Based on ongoing review of safety data, an ad hoc further formal safety analysis was conducted after 90 patients were recruited. A trial halt was recommended based on this analysis, due to a potential imbalance of venous thromboembolic events in the treatment arm, and in absence of clear evidence of treatment efficacy.

Background therapy:

Patients received full medical and surgical treatment for their injuries, including in the pre-hospital setting, resuscitation room, operating theatre, intensive care unit, and on the wards.

Evidence for comparator:

1) Pre-clinical data showing a reduction in organ failure following severe haemorrhage (published, Sordi et al. Annals of Surgery 2016), summarised below:

Pre-clinical studies showed that intravenous injection of small doses of Artesunate (1-10 mg/kg) upon resuscitation after severe haemorrhage (rat model) reduced multiple organ failure by enhancing the resistance of organs against injury. This was achieved by a) activating well-known cell-survival pathways, and b) reducing excessive inflammation.

2) Extensive data from human studies of Artesunate in severe malaria demonstrated a favourable safety profile in a critically ill cohort of patients.

Actual start date of recruitment	23 March 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	9
Adults (18-64 years)	75
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment occurred during the following periods:
21/03/2017 - 31/04/2017
30/09/2017 - 30/06/2018
14/11/2018 -15/05/2019

Pre-assignment

Screening details:

Screened = 211.
Excluded as ineligible = 106 (Age<16 = 2, Injury>2h = 34, Breastfeeding/Pregnant = 3, Code red downgraded = 6, IMP>4h from injury = 3, MHP activation >1h=5, mortality <48h = 9, non-haemorrhagic = 34, severe TBI = 10).
Eligible but not randomised = 15 (out of hours = 8, missed = 5, researcher busy = 2).
Total randomised = 90

Period 1

Period 1 title	Per Protocol (PP) Population
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The trial participant, clinical team providing treatment (including pharmacy), research investigators and outcome assessors were blind to group allocation. However, the research investigator who administered the IMP was unblinded due to the slight difference in opalescence of the IMP solution and placebo, and the requirement to visualise the IMP to confirm adequate re-constitution.

Arms

Are arms mutually exclusive?	No
Arm title	PP Placebo

Arm description:

The placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Arm type	Placebo
Investigational medicinal product name	Phosphate buffer diluent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The required volume of placebo (phosphate buffer solution only) was calculated to the same volume as if the patient received a dose of active IMP (2.4mg/kg or 4.8mg/kg depending on the stage of the study). This was administered as a single intravenous bolus dose over a period of 1-2 minutes.

Arm title	PP Artesunate (Total)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects received either 2.4mg/kg or 4.8mg/kg depending on whether they were randomised during the Low Dose or High Dose phase of the study.

Arm type	Active comparator

Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 2.4mg/kg or 4.8mg/kg depending on the stage of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Arm title	PP Artesunate (Low Dose)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 2.4 mg/kg.

Arm type	Active comparator
Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 2.4mg/kg for this arm of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Arm title	PP Artesunate (High Dose)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 4.8 mg/kg.

Arm type	Active comparator
Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 4.8 mg/kg for this arm of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Number of subjects in period 1	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)
Started	27	48	31
Completed	27	48	31

Number of subjects in period 1	PP Artesunate (High Dose)
Started	17
Completed	17

Period 2

Period 2 title	Total Randomised
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The trial participant, clinical team providing treatment (including pharmacy), research investigators and outcome assessors were blind to group allocation. However, the research investigator who administered the IMP was unblinded due to the slight difference in opalescence of the IMP solution and placebo, and the requirement to visualise the IMP to confirm adequate re-constitution.

Arms

Are arms mutually exclusive?	Yes
Arm title	Total Randomised Placebo

Arm description:

The placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Arm type	Placebo
Investigational medicinal product name	Phosphate buffer diluent
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The required volume of placebo (phosphate buffer solution only) was calculated to the same volume as if the patient received a dose of active IMP (2.4mg/kg or 4.8mg/kg depending on the stage of the study). This was administered as a single intravenous bolus dose over a period of 1-2 minutes.

Arm title	Total Randomised Artesunate (Total)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects received either 2.4mg/kg or 4.8mg/kg depending on whether they were randomised during the Low Dose or High Dose phase of the study.

Arm type	Active comparator

Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 2.4mg/kg or 4.8mg/kg depending on the stage of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Arm title	Total Randomised Artesunate (Low Dose)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 2.4 mg/kg.

Arm type	Active comparator
Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 2.4mg/kg for this arm of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Arm title	Total Randomised Artesunate (High Dose)

Arm description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 4.8 mg/kg.

Arm type	Active comparator
Investigational medicinal product name	Artesunate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

The dose of Artesunate was 4.8 mg/kg for this arm of the study and was administered as a single dose. It was necessary to reconstitute the IMP (by mixing of the phosphate buffer solution and the dry-filled Artesunate) immediately prior to administration. This was due to the inherent instability of Artesunate in aqueous solutions. After reconstitution, the IMP was administered as a single intravenous bolus dose, over 1-2 minutes.

Number of subjects in period 2	Total Randomised Placebo	Total Randomised Artesunate (Total)	Total Randomised Artesunate (Low Dose)
Started	31	59	37
Completed	27	48	31
Not completed	4	11	6
Consent withdrawn by subject	-	5	4
Protocol deviation	4	6	2

Number of subjects in period 2	Total Randomised Artesunate (High Dose)
Started	22
Completed	17
Not completed	5
Consent withdrawn by subject	1
Protocol deviation	4

Baseline characteristics

Reporting groups[1]	
Reporting group title	PP Placebo

Reporting group description:

The placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Reporting group title	PP Artesunate (Total)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects received either 2.4mg/kg or 4.8mg/kg depending on whether they were randomised during the Low Dose or High Dose phase of the study.

Reporting group title	PP Artesunate (Low Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 2.4 mg/kg.

Reporting group title	PP Artesunate (High Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 4.8 mg/kg.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The main population for analysis in this study is the per protocol population (as stipulated in the Statistical Analysis Plan, version 2.0, dated 6/8/2018). This population excludes those who were randomised and subsequently withdrawn due to protocol violations, and those who withdrew consent.

Reporting group values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)
Number of subjects	27	48	31
Age categorical Units: Subjects			
Age continuous Units: years			
median	30	29	29
inter-quartile range (Q1-Q3)	18 to 54	20 to 41	19 to 39
Gender categorical			
Gender			
Units: Subjects			
Female	0	9	6
Male	27	39	25
Mechanism of Injury Units: Subjects			
Blunt	12	25	17
Penetrating	15	23	14

Injury Severity Score			
Units: Scale			
median	20	22	25
inter-quartile range (Q1-Q3)	9 to 34	13 to 31	13 to 34
Time to admission (mins)			
Units: minute			
median	88	71	74
inter-quartile range (Q1-Q3)	55 to 102	47 to 93	48 to 94
GCS at admission			
Glasgow Coma Score			
Units: Scale			
median	15	14	14
inter-quartile range (Q1-Q3)	14 to 15	11 to 15	9 to 15
HR at admission (bpm)			
Heart Rate			
Units: beats per minute			
median	110	114	118
inter-quartile range (Q1-Q3)	88 to 123	97 to 126	105 to 128
Systolic BP at admission (mmHg)			
Units: mmHg			
median	89	100	103
inter-quartile range (Q1-Q3)	71 to 115	71 to 112	76 to 114
BE at admission (mmol/L)			
Base Excess			
Units: mmol/L			
median	-4.7	-9.0	-9.5
inter-quartile range (Q1-Q3)	-9.4 to -3.3	-12.8 to -4.9	-13.1 to -4.9
RBCs in 24 hours			
Red blood cells			
Units: units			
median	6	5	6
inter-quartile range (Q1-Q3)	4 to 8	4 to 9	4 to 9
Total blood products in 24h			
Units: units			
median	16	13	15
inter-quartile range (Q1-Q3)	10 to 19	9 to 26	10 to 23

Reporting group values	PP Artesunate (High Dose)	Total	
Number of subjects	17	75	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
median	32		
inter-quartile range (Q1-Q3)	23 to 49	-	
Gender categorical			
Gender			
Units: Subjects			
Female	3	9	
Male	14	66	

Mechanism of Injury Units: Subjects			
Blunt	8	37	
Penetrating	9	38	
Injury Severity Score Units: Scale			
median	22		
inter-quartile range (Q1-Q3)	14 to 27	-	
Time to admission (mins) Units: minute			
median	69		
inter-quartile range (Q1-Q3)	46 to 90	-	
GCS at admission			
Glasgow Coma Score			
Units: Scale			
median	14		
inter-quartile range (Q1-Q3)	12 to 15	-	
HR at admission (bpm)			
Heart Rate			
Units: beats per minute			
median	109		
inter-quartile range (Q1-Q3)	79 to 123	-	
Systolic BP at admission (mmHg) Units: mmHg			
median	90		
inter-quartile range (Q1-Q3)	65 to 112	-	
BE at admission (mmol/L)			
Base Excess			
Units: mmol/L			
median	-8.7		
inter-quartile range (Q1-Q3)	-11.2 to -5.0	-	
RBCs in 24 hours			
Red blood cells			
Units: units			
median	4		
inter-quartile range (Q1-Q3)	1 to 10	-	
Total blood products in 24h Units: units			
median	12		
inter-quartile range (Q1-Q3)	7 to 29	-	

Subject analysis sets

Subject analysis set title	ITT Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Placebo population includes everyone who was randomised to the Placebo arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (Total)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Total) population includes everyone who was randomised to the Artesunate arms (Low Dose/High Dose), including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (Low Dose)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Low Dose) population includes everyone who was randomised to the Artesunate (Low Dose) arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (High Dose)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Low Dose) population includes everyone who was randomised to the Artesunate (Low Dose) arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	Safety Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP are not included in this population. Patients were analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (Total)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (Low Dose)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (High Dose)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Reporting group values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)
Number of subjects	31	54	33
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
median	26	29	29
inter-quartile range (Q1-Q3)	18 to 53	20 to 40	19 to 39
Gender categorical			
Gender			
Units: Subjects			
Female	1	10	7
Male	30	44	26

Mechanism of Injury Units: Subjects			
Blunt	12	27	18
Penetrating	19	27	15
Injury Severity Score Units: Scale			
median	16	19	22
inter-quartile range (Q1-Q3)	9 to 29	13 to 29	13 to 34
Time to admission (mins) Units: minute			
median	86	69	74
inter-quartile range (Q1-Q3)	55 to 100	53 to 91	53 to 93
GCS at admission			
Glasgow Coma Score			
Units: Scale			
median	15	14	14
inter-quartile range (Q1-Q3)	14 to 15	11 to 15	9 to 15
HR at admission (bpm)			
Heart Rate			
Units: beats per minute			
median	110	113	118
inter-quartile range (Q1-Q3)	88 to 118	97 to 127	105 to 129
Systolic BP at admission (mmHg) Units: mmHg			
median	85	100	103
inter-quartile range (Q1-Q3)	71 to 110	71 to 110	80 to 110
BE at admission (mmol/L)			
Base Excess			
Units: mmol/L			
median	-4.7	-9.1	-9.5
inter-quartile range (Q1-Q3)	-7.5 to -3.5	-13.1 to -4.9	-13.1 to -4.9
RBCs in 24 hours			
Red blood cells			
Units: units			
median	6	5	6
inter-quartile range (Q1-Q3)	4 to 8	3 to 10	4 to 9
Total blood products in 24h Units: units			
median	15	13	14
inter-quartile range (Q1-Q3)	10 to 19	9 to 26	10 to 21

Reporting group values	ITT Artesunate (High Dose)	Safety Placebo	Safety Artesunate (Total)
Number of subjects	21	29	54
Age categorical Units: Subjects			

Age continuous Units: years			
median	29	26	28
inter-quartile range (Q1-Q3)	23 to 40	18 to 53	20 to 39

Gender categorical			
Gender			
Units: Subjects			
Female	3	0	9
Male	18	29	45
Mechanism of Injury Units: Subjects			
Blunt	9	12	26
Penetrating	12	17	28
Injury Severity Score Units: Scale			
median	19	17	22
inter-quartile range (Q1-Q3)	9 to 27	9 to 29	13 to 29
Time to admission (mins) Units: minute			
median	64	86	69
inter-quartile range (Q1-Q3)	53 to 90	55 to 100	48 to 91
GCS at admission			
Glasgow Coma Score			
Units: Scale			
median	14	15	14
inter-quartile range (Q1-Q3)	12 to 15	13 to 15	12 to 15
HR at admission (bpm)			
Heart Rate			
Units: beats per minute			
median	109	110	113
inter-quartile range (Q1-Q3)	82 to 123	88 to 118	97 to 127
Systolic BP at admission (mmHg) Units: mmHg			
median	90	85	96
inter-quartile range (Q1-Q3)	70 to 110	70 to 115	71 to 110
BE at admission (mmol/L)			
Base Excess			
Units: mmol/L			
median	-8.9	-4.8	-8.9
inter-quartile range (Q1-Q3)	-13.0 to -5.0	-8.4 to -3.4	-12.5 to -4.9
RBCs in 24 hours			
Red blood cells			
Units: units			
median	4	6	5
inter-quartile range (Q1-Q3)	1 to 11	4 to 8	4 to 9
Total blood products in 24h Units: units			
median	12	16	13
inter-quartile range (Q1-Q3)	6 to 29	10 to 19	9 to 27

Reporting group values	Safety Artesunate (Low Dose)	Safety Artesunate (High Dose)	
Number of subjects	34	20	
Age categorical Units: Subjects			

Age continuous			
Units: years			
median	28	28	
inter-quartile range (Q1-Q3)	19 to 37	21 to 45	
Gender categorical			
Gender			
Units: Subjects			
Female	6	3	
Male	28	17	
Mechanism of Injury			
Units: Subjects			
Blunt	18	8	
Penetrating	16	12	
Injury Severity Score			
Units: Scale			
median	24	19	
inter-quartile range (Q1-Q3)	13 to 34	10 to 27	
Time to admission (mins)			
Units: minute			
median	74	63	
inter-quartile range (Q1-Q3)	57 to 93	45 to 89	
GCS at admission			
Glasgow Coma Score			
Units: Scale			
median	14	14	
inter-quartile range (Q1-Q3)	10 to 15	12 to 15	
HR at admission (bpm)			
Heart Rate			
Units: beats per minute			
median	118	110	
inter-quartile range (Q1-Q3)	102 to 129	77 to 125	
Systolic BP at admission (mmHg)			
Units: mmHg			
median	101	90	
inter-quartile range (Q1-Q3)	72 to 110	70 to 110	
BE at admission (mmol/L)			
Base Excess			
Units: mmol/L			
median	-8.8	-8.9	
inter-quartile range (Q1-Q3)	-12.5 to -4.9	-15.3 to -5.0	
RBCs in 24 hours			
Red blood cells			
Units: units			
median	6	4	
inter-quartile range (Q1-Q3)	4 to 9	1 to 11	
Total blood products in 24h			
Units: units			
median	14	13	
inter-quartile range (Q1-Q3)	10 to 23	7 to 30	

End points

End points reporting groups

Reporting group title	PP Placebo

Reporting group description:

The placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Reporting group title	PP Artesunate (Total)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects received either 2.4mg/kg or 4.8mg/kg depending on whether they were randomised during the Low Dose or High Dose phase of the study.

Reporting group title	PP Artesunate (Low Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 2.4 mg/kg.

Reporting group title	PP Artesunate (High Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 4.8 mg/kg.

Reporting group title	Total Randomised Placebo

Reporting group description:

The placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Reporting group title	Total Randomised Artesunate (Total)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects received either 2.4mg/kg or 4.8mg/kg depending on whether they were randomised during the Low Dose or High Dose phase of the study.

Reporting group title	Total Randomised Artesunate (Low Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 2.4 mg/kg.

Reporting group title	Total Randomised Artesunate (High Dose)

Reporting group description:

Artesunate provided as a white crystalline powder in a glass vial containing 110mg, supplied with a second glass vial of reconstitution diluent which is a sterile phosphate buffer.

Subjects were dosed at 4.8 mg/kg.

Subject analysis set title	ITT Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Placebo population includes everyone who was randomised to the Placebo arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (Total)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Total) population includes everyone who was randomised to the Artesunate arms (Low Dose/High Dose), including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (Low Dose)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Low Dose) population includes everyone who was randomised to the Artesunate (Low Dose) arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	ITT Artesunate (High Dose)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Artesunate (Low Dose) population includes everyone who was randomised to the Artesunate (Low Dose) arm, including those who actually received a different treatment than allocated, and those who did not survive or otherwise had no SOFA score at 48h.

Subject analysis set title	Safety Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP are not included in this population. Patients were analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (Total)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (Low Dose)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Subject analysis set title	Safety Artesunate (High Dose)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all the patients who were randomised and received any partial dose of IMP. Those patients that did not receive any dose of IMP will not be included in this population. Patients will be analysed based on actual treatment received.

Primary: 48-hour SOFA Score

End point title	48-hour SOFA Score

End point description:

48-hour SOFA score

End point type	Primary

End point timeframe:

48 hours from admission

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	4 (2 to 8)	5.5 (2.5 to 10.5)	6 (2 to 11)	5 (3 to 10)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	50	33	17
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	4 (2 to 8)	5 (3 to 10)	5 (3 to 10)	5 (3 to 10)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.303
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.9

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.411
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.326
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.211
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.7

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262
Method	Wilcoxon (Mann-Whitney)

Primary: 48-hour SOFA Score (mean values)

End point title	48-hour SOFA Score (mean values)[1]

End point description:

48-hour SOFA Score (mean values)

End point type	Primary

End point timeframe:

48 hours

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: This is a duplicate primary end-point data field in order to report the mean value (in addition to the median values that are already reported). In the SAP, we stated that we would report both the median and the mean central tendencies for the primary outcome measure. The statistical analysis for the primary endpoint is reported under the median value (non-parametric comparison).

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: SOFA Score				
arithmetic mean (inter-quartile range (Q1-Q3))	5.3 (2.0 to 8.0)	6.4 (2.5 to 10.5)	6.3 (2.0 to 11.0)	6.7 (3.0 to 10.0)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	50	33	17
Units: SOFA Score				
arithmetic mean (inter-quartile range (Q1-Q3))	5.1 (2.0 to 8.0)	6.3 (3.0 to 10.0)	6.2 (3.0 to 10.0)	6.7 (3.0 to 10.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Max SOFA

End point title	Max SOFA

End point description:

Maximum SOFA score during studied period

End point type	Secondary

End point timeframe:
Admission to Day 7, Day 28

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	9 (4 to 10)	10 (5 to 12.5)	10 (5 to 12)	10 (4 to 13)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	52	33	19
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	8 (4 to 10)	10 (5 to 12)	10 (5 to 12)	9 (4 to 13)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.7

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.345
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.3

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Wilcoxon (Mann-Whitney)

Secondary: Mean SOFA Score

End point title	Mean SOFA Score

End point description:

Mean SOFA score calculated using scores recorded on days 2-5.
Imputations were not performed for missing SOFA scores within this timeframe (e.g. due to death/early discharge) as per the Statistical Analysis Plan (version 2.0, dated 6/8/2018). Patients with missing SOFA scores during this timeframe were therefore excluded from the analysis .

End point type	Secondary

End point timeframe:

Day 2 to Day 5

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	3.3 (2.0 to 8.3)	5.9 (2.3 to 9.0)	5.0 (2.5 to 9.0)	6.3 (1.8 to 8.8)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	50	33	17
Units: SOFA Score				
median (inter-quartile range (Q1-Q3))	3.0 (2.0 to 7.5)	5.9 (2.5 to 9.0)	5.0 (2.5 to 9.0)	6.3 (1.8 to 8.8)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)

Statistical analysis description:

Per Protocol Analysis

Comparison groups	PP Placebo v PP Artesunate (Total)

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.536
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	1.1

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.569
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.638
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	0.8

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Low High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.531
Method	Wilcoxon (Mann-Whitney)

Secondary: CTCOFR Score	
End point title	CTCOFR Score
End point description: Composite time to organ failure resolution score.	
End point type	Secondary
End point timeframe: Admission to Day 14	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: CTCOFR Score				
median (inter-quartile range (Q1-Q3))	4 (0 to 15)	5 (0 to 15)	6 (0 to 15)	4 (1 to 13)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: CTCOFR Score				
median (inter-quartile range (Q1-Q3))	4 (0 to 15)	5 (0 to 15)	6 (0 to 15)	4 (0 to 15)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	3.6

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.701
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.667
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2.8

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.989
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.992
Method	Wilcoxon (Mann-Whitney)

Secondary: Ventilator Free Days	
End point title	Ventilator Free Days

End point description:

Number of days free from mechanical ventilation out of 28 days

End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: day				
median (inter-quartile range (Q1-Q3))	26 (12 to 28)	25 (16 to 28)	25 (14 to 28)	26 (19 to 28)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: day				
median (inter-quartile range (Q1-Q3))	26 (12 to 28)	25 (16 to 28)	25 (15 to 28)	26 (18 to 28)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	3.2

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.474
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.825
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	3.7

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.917
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758
Method	Wilcoxon (Mann-Whitney)

Secondary: Hospital LOS

End point title	Hospital LOS
End point description: Hospital Length of Stay	
End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: day				
median (inter-quartile range (Q1-Q3))	28 (10 to 52)	25 (9 to 42)	25 (9 to 43)	26 (9 to 41)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: day				
median (inter-quartile range (Q1-Q3))	23 (9 to 49)	23 (8 to 40)	25 (10 to 40)	17 (7 to 37)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	14.6

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.838
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.891
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.3
upper limit	12.6

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.677
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.391
Method	Wilcoxon (Mann-Whitney)

Secondary: ACCU LOS	
End point title	ACCU LOS
End point description: Length of stay on the adult critical care unit	
End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: day				
median (inter-quartile range (Q1-Q3))	11 (3 to 24)	8 (5 to 18.5)	8 (5 to 19)	9 (3 to 18)

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: day				
median (inter-quartile range (Q1-Q3))	5 (3 to 22)	7.5 (4 to 18)	8 (5 to 19)	6 (0 to 18)

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description:	
Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.736
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	16.2

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description:	
Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description:	
Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.629
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	13.7

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	Wilcoxon (Mann-Whitney)

Secondary: Infection	
End point title	Infection
End point description: Incidence of Infection	
End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: Infection				
Infection	11	19	11	8
No Infection	16	29	20	9

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: Infection				
Infection	11	21	13	8
No Infection	20	33	20	13

Statistical analyses

Statistical analysis title	Placebo versus Artesunate (Total)
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Chi-squared

Statistical analysis title	Placebo versus Artesunate (Low Dose)
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	Chi-squared

Statistical analysis title	Placebo versus Artesunate (High Dose)
Comparison groups	PP Placebo v PP Artesunate (Low Dose)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.755
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.747
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	Chi-squared

Secondary: Acute Lung Injury	
End point title	Acute Lung Injury
End point description: Incidence of Acute Lung Injury (Defined as Mild/Moderate/Severe according to Berline Definition)	
End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: ALI				
ALI	20	31	20	11
No ALI	7	17	11	8

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	52	33	19
Units: ALI				
ALI	20	32	21	11
No ALI	11	20	12	8

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.398
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.433
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.507
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.786
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.942
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Chi-squared

Secondary: Acue Kidney Injury	
End point title	Acue Kidney Injury
End point description: Incidence of acute kidney injury (defined as RIFLE Score of 2 or greater)	
End point type	Secondary
End point timeframe: Admission to Day 28	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: AKI				
AKI	20	40	25	15
No AKI	17	8	6	2

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	51	33	18
Units: AKI				
AKI	22	43	27	16
No AKI	9	8	6	2

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.549
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.257
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.306
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.147
Method	Chi-squared

Secondary: Prolonged Multiple Organ Dysfunction Syndrome	
End point title	Prolonged Multiple Organ Dysfunction Syndrome
End point description: Incidence of patients with a SOFA>5 on Day 7 after admission	
End point type	Secondary
End point timeframe: Day 7	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26[2]	47[3]	30[4]	17
Units: PRMODS				
PRMODS	6	10	6	4
No PRMODS	20	37	24	13

Notes:

[2] - 1 patient excluded as died<7 days

[3] - 1 patient excluded as died<7 days

[4] - 1 patient excluded as died<7 days

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	51	32	19
Units: PRMODS				
PRMODS	6	11	7	4
No PRMODS	23	49	25	15

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.859
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.973
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.941
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.897
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.976
Method	Chi-squared

Secondary: Mortality (28-day)	
End point title	Mortality (28-day)
End point description: Mortality at 28 days	
End point type	Secondary
End point timeframe: Admission to 28 days	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: Mortality				
Dead	1	2	2	0
Alive	26	46	29	17

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: Mortality				
Dead	2	4	2	2
Alive	29	50	31	19

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 949
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Chi-squared

Secondary: Mortality (discharge)	
End point title	Mortality (discharge)
End point description: Mortality at discharge	
End point type	Secondary
End point timeframe: Admission to discharge	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: mortality				
Dead	1	2	2	0
Alive	26	46	29	0

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: mortality				
Dead	2	4	2	2
Alive	29	50	31	19

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dosel)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Chi-squared

Secondary: Mortality (90 day)	
End point title	Mortality (90 day)
End point description: Mortality at 90 days after admission	
End point type	Secondary
End point timeframe: Admission to 90 days	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: mortality				
Dead	1	2	1	0
Alive	26	46	30	17

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: mortality				
Dead	2	4	2	2
Alive	29	50	31	19

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.922
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Chi-squared

Secondary: Alive and Free of MODS	
End point title	Alive and Free of MODS
End point description: Patients who are still alive and free of MODS at the end of 48 hours	
End point type	Secondary
End point timeframe: Admission to 48 hours	

End point values	PP Placebo	PP Artesunate (Total)	PP Artesunate (Low Dose)	PP Artesunate (High Dose)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	48	31	17
Units: MODS				
Alive and free of MODS	18	24	15	9
Dead or ongoing MODS	9	24	16	8

End point values	ITT Placebo	ITT Artesunate (Total)	ITT Artesunate (Low Dose)	ITT Artesunate (High Dose)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	54	33	21
Units: MODS				
Alive and free of MODS	21	28	17	11
Dead or ongoing MODS	10	26	16	10

Statistical analyses

Statistical analysis title	PP Placebo versus Artesunate (Total)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Total)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (Low Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (Low Dose)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161
Method	Chi-squared

Statistical analysis title	PP Placebo versus Artesunate (High Dose)
Statistical analysis description: Per Protocol Analysis	
Comparison groups	PP Placebo v PP Artesunate (High Dose)

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.363
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Total)
Comparison groups	ITT Placebo v ITT Artesunate (Total)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (Low Dose)
Comparison groups	ITT Placebo v ITT Artesunate (Low Dose)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.187
Method	Chi-squared

Statistical analysis title	ITT Placebo versus Artesunate (High Dose)
Comparison groups	ITT Placebo v ITT Artesunate (High Dose)
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.683
Method	Chi-squared

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Daily from admission to day 28

Adverse event reporting additional description:

Clinical research fellows assessed patients for adverse events (AEs) and serious adverse events (SAEs) daily during the monitored study period (admission to day 28). All SAEs were formally recorded on an SAE proforma. The clinical fellow also maintained a daily log of all AEs and followed these up daily to assess for any development into an SAE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Placebo (Safety Population)

Reporting group description:

Placebo comprises buffered diluent drawn up to the volume that would be necessary to reconstitute active IMP according to the subjects' weight.

Reporting group title	Artesunate (Total) (Safety Population)

Reporting group description:

This group comprises all patients who received any partial or complete dose of Artesunate.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The study cohort consisted of severely injured trauma patients with major haemorrhage and due to the nature of their injuries, they sustain a high volume of adverse events during the course of their admission. It was therefore agreed with the study sponsor that AEs would be logged by the study team for follow up (to determine if they subsequently develop into SAEs), however formal reporting was not required.

Serious adverse events	Placebo (Safety Population)	Artesunate (Total) (Safety Population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	17 / 54 (31.48%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Surgical and medical procedures			
Iatrogenic vascular injury	Additional description: Iatrogenic vascular injury to L CFA related to REBOA guidewire - thrombus wtihin the left CFA, PFA and R CIA		
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Nervous system disorders			
Neurological	Additional description: 1 patient with critical care neuropathy (placebo arm) 1 patient with a cerebral event (tiny cerebral foci of unclear cause)		
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thromboembolic			
subjects affected / exposed	1 / 29 (3.45%)	9 / 54 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Organ failure			
subjects affected / exposed	1 / 29 (3.45%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fulminant organ failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 29 (3.45%)	2 / 54 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rhabdomyolysis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection	Additional description: Presence of infection as defined by the criteria by Cole et al., 2014 (Appendix 2 of the Protocol, version 2.1, dated 24/2/2017)		
subjects affected / exposed	2 / 29 (6.90%)	2 / 54 (3.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (Safety Population)	Artesunate (Total) (Safety Population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 29 (0.00%)	0 / 54 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2016	*Amendment prior to trial start date Change of IMP batch - shelf life stability of diluent. Informed consent - clarity for deceased patients.
25 April 2017	*Prior to trial start date Amendement to study co-enrolment policy and inclusion criteria. Change of trial statistician.
29 March 2018	IMPD Update: Alteration of inclusion criteria Change of stability protocol Change of batch number Change of label format
28 May 2019	Trial halt- Following a review of trial data during an interim analysis, after enrolment of 75 of the 105 total planned study subjects for the per protocol analysis, the Trial Steering Committee recommended the trial should be terminated early. This was based on the safety analysis performed by the Data Monitoring Committee, which identified the possibility of an increased rate of thrombotic events in the artesunate arm of the trial compared to the placebo arm. The primary outcome analysis at this stage did not identify a treatment benefit to justify continuing the trial to completion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 May 2017	IMP expired - awaiting new batch delivery	29 September 2017
01 July 2018	Interim Analysis	14 November 2018

Notes:

Limitations and caveats

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

The trial was halted early leading to a reduced sample size.

Notes: