Clinical trial results:
Randomized double blind placebo-controlled clinical safety, tolerability and pharmacokinetic/-dynamic study on the effects of escalating single intravenous doses of EA-230 on the innate immune response during experimental human endotoxemia

Summary

EudraCT number	2014-002481-78
Trial protocol	NL
Global end of trial date	26 June 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021
Summary attachment (see zip file)	A randomized doubleblind, placebocontrolled clinical phase IIa trial on safety, immunomodulatory effects and pharmacokinetics of EA230 during experimental human endotoxaemia (BCP-85-1559.pdf)

Trial information

Trial identification

Sponsor protocol code	EBI-EA230-LPS-2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	Geert Grooteplein 10, Nijmegen, Netherlands, 6500 HB
Public contact	Lucas van Eijk, Radboud UMC, Research Intensive care, lucas.vanEijk@radboudumc.nl
Scientific contact	Lucas van Eijk, Radboud UMC, Research Intensive care, lucas.vanEijk@radboudumc.nl

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	15 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2015
Global end of trial reached?	Yes
Global end of trial date	26 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: To assess the safety, tolerability and pharmacokinetic-dynamic response, of single escalating doses of EA-230 in healthy subjects.

Part 2: To assess the dose-and plasma concentration-response relation of single escalating doses EA-230 on inflammation and LPS-induced changes in markers for renal function, and to assess safety, tolerability and PK of EA-230 under the condition of experimental endotoxemia.

Protection of trial subjects:

All subjects provided informed consent. Safety and tolerability assessments were performed continuously from the start of study drug treatment until 8 hours afterwards and at 4 consecutive study visits during the 14day followup period. Safety parameters included vital signs (blood pressure and heart rate), 12lead ECG and routine laboratory haematology and biochemistry. AEs were recorded throughout the complete study period. All AEs were judged by the investigator with regard to severity (mild, moderate or severe) according to Common Terminology Criteria for Adverse Events guidelines 4.0,36 and their relation to the study drug (definitely related, probably related, possibly related, unlikely to be related or unrelated). LPSinduced flulike symptoms were scored separately, as explained below, and for practical considerations excluded from safety analyses. SAEs included death, lifethreatening, persistent and/or significant disability and/or incapacity and hospitalization and/or prolongation of inpatient hospitalization. Safety parameters were reported to and reviewed by an independent Data Safety Monitoring Board (DSMB) after completion of each dosing group.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 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	Netherlands: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

36 healthy adult males enrolled

Pre-assignment

Screening details:

Health status of the participants was determined by medical history, physical examination, electrocardiogram (ECG) and routine laboratory blood tests.

Period 1

Period 1 title	Full study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	EA-230, 15 mg/kg/h

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EA-230
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg/h

Arm title	EA-230, 45 mg/kg/h

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EA-230
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

45 mg/kg/h

Arm title	EA-230, 90 mg/kg/h

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EA-230
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/kg/h

Arm title	Placebo

Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Sodium chloride solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Osmolar equivalent of 29 mg/mL sodium chloride solution

Number of subjects in period 1	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h
Started	8	8	8
Completed	8	8	8

Number of subjects in period 1	Placebo
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	EA-230, 15 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 45 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 90 mg/kg/h
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h
Number of subjects	8	8	8
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	8
Gender categorical Units: Subjects			
Male	8	8	8

Reporting group values	Placebo	Total	
Number of subjects	12	36	
Age categorical Units: Subjects			
Adults (18-64 years)	12	36	
Gender categorical Units: Subjects			
Male	12	36	

End points

End points reporting groups

Reporting group title	EA-230, 15 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 45 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 90 mg/kg/h
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Safety and tolerability of EA-230

End point title	Safety and tolerability of EA-230[1]

End point description:

End point type	Primary

End point timeframe:

During complete study period

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: No statistical analysis was performed as this concerns safety data.

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	12
Units: (Severe) adverse events				
Severe adverse events	2	2	3	7
Adverse events	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Effects of EA230 on circulating levels of inflammatory mediators and adhesion molecules during endotoxaemia

End point title	Effects of EA230 on circulating levels of inflammatory mediators and adhesion molecules during endotoxaemia

End point description:

End point type	Secondary

End point timeframe:

Ethylenediaminetetraacetic acid (EDTA)anticoagulated blood samples for measurement of inflammatory parameters were obtained at time points t = 0, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	12
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))				
IL-6	2433 (872 to 4700)	1671 (869 to 2960)	797 (372 to 1730)	1768 (914 to 2435)
TNFa	145 (76 to 202)	116 (64 to 163)	100 (72 to 150)	121 (86 to 160)
IL-10	346 (277 to 421)	451 (173 to 623)	529 (183 to 1089)	454 (301 to 653)
IL-8	957 (773 to 1107)	1123 (699 to 1454)	1034 (713 to 1137)	544 (474 to 893)
MCP-1	7902 (7558 to 11029)	12238 (6480 to 12632)	8234 (5867 to 10847)	5328 (4743 to 10038)

Statistical analyses

Statistical analysis title	Differences over time
Comparison groups	EA-230, 90 mg/kg/h v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Repeated measures 2way ANOVA (interacti

Secondary: Effects of EA230 on leucocyte counts and differentiation during endotoxaemia

End point title	Effects of EA230 on leucocyte counts and differentiation during endotoxaemia

End point description:

End point type	Secondary

End point timeframe:

EDTA anticoagulated blood samples were obtained at time points t = −1, 0, 1, 2, 4, 8, 24 and 48 hours

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	12
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))				
Leucocytes	10.1 (8.5 to 12.0)	12.5 (10.7 to 14.6)	11.8 (10.6 to 15.7)	10.3 (7.8 to 12.2)
Neutrophils	12.9 (10.5 to 16.3)	15.2 (13.2 to 17.4)	16.2 (12.4 to 18.0)	13.3 (9.8 to 15.2)
Lymphocytes	3.9 (2.6 to 4.8)	3.7 (2.6 to 5.5)	3.0 (2.5 to 4.7)	4.2 (3.3 to 5.3)
Monocytes	1.1 (0.7 to 1.5)	1.3 (1.1 to 1.8)	1.0 (0.9 to 1.2)	1.0 (0.9 to 1.5)

Statistical analyses

Statistical analysis title	Differences over time
Comparison groups	EA-230, 15 mg/kg/h v EA-230, 45 mg/kg/h v EA-230, 90 mg/kg/h v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Repeated measures 2way ANOVA (interacti

Secondary: Effects of EA230 on vital signs and symptoms during endotoxaemia (body temperature)

End point title	Effects of EA230 on vital signs and symptoms during endotoxaemia (body temperature)

End point description:

End point type	Secondary

End point timeframe:

Every 30 minutes, temperature was measured from t=0 to t=8 (hours) after endotoxin administration

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	12
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))	529 (527 to 530)	529 (524 to 534)	529 (525 to 534)	530 (526 to 534)

Statistical analyses

Statistical analysis title	Differences over time
Comparison groups	EA-230, 15 mg/kg/h v EA-230, 45 mg/kg/h v EA-230, 90 mg/kg/h v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Repeated measures 2way ANOVA (interacti

Secondary: Effects of EA230 on vital signs and symptoms during endotoxaemia (symptom score)

End point title	Effects of EA230 on vital signs and symptoms during endotoxaemia (symptom score)

End point description:

End point type	Secondary

End point timeframe:

LPSinduced flulike symptoms were scored per symptom every 30 minutes from t=0 to t=8 (hours) after endotoxin administration

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	8	12
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))				
total symptom score	11.0 (3.5 to 23.5)	15.5 (8.3 to 22.1)	6.0 (4.0 to 12.0)	19.5 (9.0 to 27.4)

Statistical analyses

Statistical analysis title	Differences over time
Comparison groups	EA-230, 15 mg/kg/h v EA-230, 45 mg/kg/h v EA-230, 90 mg/kg/h v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Repeated measures 2way ANOVA (interacti

Secondary: Pharmacokinetics of EA230 during endotoxaemia (AUC, 0-last)

End point title	Pharmacokinetics of EA230 during endotoxaemia (AUC, 0-last)[2]

End point description:

End point type	Secondary

End point timeframe:

t = 0 to the time of the last measured concentration

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No drug was adminstered in the baseline period yet, so no need for statistical comparison.

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: h.ug/L				
geometric mean (confidence interval 95%)	2672 (2097 to 3403)	7647 (5431 to 10766)	19658 (15428 to 25046)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of EA230 during endotoxaemia (AUC, 0-inf)

End point title	Pharmacokinetics of EA230 during endotoxaemia (AUC, 0-inf)[3]

End point description:

End point type	Secondary

End point timeframe:

t = 0 to infinity extrapolated

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: No drug was adminstered in the baseline period yet, so no need for statistical comparison.

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	5	8	
Units: h.ug/L				
geometric mean (confidence interval 95%)	3349 (1244 to 9014)	6519 (4243 to 10015)	19658 (15429 to 25046)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of EA230 during endotoxaemia (Cmax)

End point title	Pharmacokinetics of EA230 during endotoxaemia (Cmax)[4]

End point description:

End point type	Secondary

End point timeframe:

Throughout complete study period

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No drug was adminstered in the baseline period yet, so no need for statistical comparison.

End point values	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	8	
Units: ug/L				
geometric mean (confidence interval 95%)	1983 (1725 to 2279)	6030 (4190 to 8676)	15657 (13100 to 18714)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the complete study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE guidelines
Dictionary version	4.0

Reporting groups	
Reporting group title	EA-230, 15 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 45 mg/kg/h
Reporting group description: -	
Reporting group title	EA-230, 90 mg/kg/h
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	EA-230, 15 mg/kg/h	EA-230, 45 mg/kg/h	EA-230, 90 mg/kg/h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	3 / 8 (37.50%)
Nervous system disorders			

Head discomfort			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Infusion site reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
upper abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Soft faeces			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
Nervous system disorders			
Head discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Infusion site reaction			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Feeling hot			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
upper abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Soft faeces			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Back pain			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	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

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

Human endotoxaemia model (model vs. clinical situation), only adult males, non-complete PK parameter dataset of subjects subjected to lower dosage EA230 group, no definite conclusions of optimal timing of EA230 administration

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30919998