Clinical trial results:
Randomized double blind placebo-controlled phase II study on the effects of EA-230 on the innate immune response following on-pump cardiac surgery

Summary

EudraCT number	2015-005600-28
Trial protocol	NL
Global end of trial date	22 February 2018

Results information

Result version number	v1 (current)
This version publication date	07 August 2022
First version publication date	07 August 2022
Summary attachment (see zip file)	Randomized double blind placebo-controlled phase II study on the effects of EA-230 on the innate immune response following on-pump cardiac surgery (2015-005600-28.pdf)

Trial information

Trial identification

Sponsor protocol code	EBI-CABG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03145220
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	Roger van Groenendael, Radboud University Medical Center, r.vangroenendael@radoudumc.nl
Scientific contact	Roger van Groenendael, Radboud University Medical Center, r.vangroenendael@radoudumc.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	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2018
Global end of trial reached?	Yes
Global end of trial date	22 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety and tolerability of EA-230 in patients undergoing cardiac surgery with cardiopulmonary bypass.
To assess the anti-inflammatory effect of EA-230 in patients with systemic inflammation following cardiac surgery.

Protection of trial subjects:

In part 1 (phase IIa) a total of 30 patients receiving active
treatment will be included.In part 2 (phase IIb) 60 patients per treatment group will be included.
After enrolment in the study, patients will be monitored for a followup time of 90 days.
After inclusion of all patients in the first study part, a report containing all the relevant safety data including (S)AE's and SUSARs will be provided to the DSMB and to the ethics committee (CMO). After unblinded analysis of all safety data, the DSMB will report an advice whether to proceed with part 2 of the study or not. Additionally, safety data will be reevaluated at a second interim analysis after a total of 90 patients have been included (including patients from both part 1 and part 2)
The ethics committee will be provided with a copy of the interim safety report along with the evaluation regarding safety parameters by the DSMB.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 179
Worldwide total number of subjects	179
EEA total number of subjects	179

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	65
From 65 to 84 years	112
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients older than 18 years scheduled for elective coronary artery bypass grafting (CABG) procedure, with or
without valve surgery, with use of CPB were eligible for participation. A standardized protocol was used for the
surgical procedure and anesthetic management. Patients that were immune-compromised were excluded.

Pre-assignment

Screening details:

440 patients assessed for eligibilit
120 declined participation
140 ineligible
- 71 immuno-acve drugs
- 19 immunocompromised
- 15 iodine-contrast allergy
- 35 other

180 patients included
- 89 randomized to receive placebo
- 90 randomized to receive EA-230,

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo

Arm description:

NaCl in water for injection, osmotic strength 8001000 mOsm/L; pH 4.57.0.
Before administration placebo will be diluted in 1000 mL NaCl 0.9% to reach an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.

Arm type	Placebo
Investigational medicinal product name	NaCl 0.9%
Investigational medicinal product code	
Other name	Normal saline
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

NaCl in water for injection, osmotic strength 8001000 mOsm/L; pH 4.57.0.
Before administration placebo will be diluted in 1000 mL NaCl 0.9% to reach an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.

Arm title	EA-230

Arm description:

300 mg/mL EA230 in water for injection; osmotic strength 8001000 mOsmol/L; pH 4.0 – 8.0. Before administration IMP will be diluted in 1000 mL NaCl 0.9% to obtain an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.

Arm type	Experimental

Investigational medicinal product name	EA-230
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

300 mg/mL EA230 in water for injection; osmotic strength 8001000 mOsmol/L; pH 4.0 – 8.0. Before administration IMP will be diluted in 1000 mL NaCl 0.9% to obtain an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.

Number of subjects in period 1	placebo	EA-230
Started	89	90
Completed	89	90

Baseline characteristics

Reporting groups	
Reporting group title	placebo
Reporting group description:	
NaCl in water for injection, osmotic strength 8001000 mOsm/L; pH 4.57.0. Before administration placebo will be diluted in 1000 mL NaCl 0.9% to reach an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	
Reporting group title	EA-230
Reporting group description:	
300 mg/mL EA230 in water for injection; osmotic strength 8001000 mOsmol/L; pH 4.0 – 8.0. Before administration IMP will be diluted in 1000 mL NaCl 0.9% to obtain an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	

Reporting group values	placebo	EA-230	Total
Number of subjects	89	90	179
Age categorical Units: Subjects			
Adults (18-64 years)	30	35	65
From 65-84 years	58	54	112
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	12	10	22
Male	77	80	157

End points

End points reporting groups

Reporting group title	placebo
Reporting group description:	
NaCl in water for injection, osmotic strength 8001000 mOsm/L; pH 4.57.0. Before administration placebo will be diluted in 1000 mL NaCl 0.9% to reach an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	
Reporting group title	EA-230
Reporting group description:	
300 mg/mL EA230 in water for injection; osmotic strength 8001000 mOsmol/L; pH 4.0 – 8.0. Before administration IMP will be diluted in 1000 mL NaCl 0.9% to obtain an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	

Primary: Adverse events

End point title	Adverse events
End point description:	
End point type	Primary
End point timeframe:	
until 90-days post-surgery	

End point values	placebo	EA-230		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90[1]		
Units: AEs				
Treatment-emergent AEs	218	217		
Treatment-emergent SAEs	19	13		
SUSARs	1	0		
Major clinical AEs related to cardiac surgery	15	11		

Notes:

[1] - 1 patients was excluded because of a last-minute decision to perform surgery without CPB

Statistical analyses

Statistical analysis title	Not applicable
Statistical analysis description:	
Not applicable as this concerns safety data.	
Comparison groups	placebo v EA-230

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 1
Method	NA

Notes:

[2] - Not applicable as this concerns safety data.

Primary: Plasma Il-6 levels

End point title	Plasma Il-6 levels

End point description:

End point type	Primary

End point timeframe:

From pre-surgery until the first postoperative day

End point values	placebo	EA-230		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90[3]		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	213 (154 to 287)	189 (141 to 293)		

Notes:

[3] - 1 patients was excluded because of a last-minute decision to perform surgery without CPB

Statistical analyses

Statistical analysis title	Comparison
Comparison groups	placebo v EA-230
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.99
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Until day 90 post-surgery (so also post-treatment)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	NA

Reporting groups	
Reporting group title	placebo
Reporting group description:	
NaCl in water for injection, osmotic strength 8001000 mOsm/L; pH 4.57.0. Before administration placebo will be diluted in 1000 mL NaCl 0.9% to reach an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	
Reporting group title	EA-230
Reporting group description:	
300 mg/mL EA230 in water for injection; osmotic strength 8001000 mOsmol/L; pH 4.0 – 8.0. Before administration IMP will be diluted in 1000 mL NaCl 0.9% to obtain an osmotic strength of <400 mOsmol/L. Start of administration at first incision until stop of ECC pump, with a maximum total infusion time of 4 hours.	

Serious adverse events	placebo	EA-230	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 89 (19.10%)	12 / 90 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
N/A			
subjects affected / exposed	2 / 89 (2.25%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
N/A			
subjects affected / exposed	6 / 89 (6.74%)	4 / 90 (4.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
N/A			

subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
N/A			
subjects affected / exposed	2 / 89 (2.25%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
N/A			
subjects affected / exposed	1 / 89 (1.12%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
N/A			
subjects affected / exposed	1 / 89 (1.12%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
N/A			
subjects affected / exposed	2 / 89 (2.25%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	placebo	EA-230	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 89 (91.01%)	78 / 90 (86.67%)	
Vascular disorders			
N/A			
subjects affected / exposed	29 / 89 (32.58%)	26 / 90 (28.89%)	
occurrences (all)	29	26	
Cardiac disorders			

N/A subjects affected / exposed occurrences (all)	45 / 89 (50.56%) 45	44 / 90 (48.89%) 44	
Nervous system disorders N/A subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 14	11 / 90 (12.22%) 11	
Blood and lymphatic system disorders N/A subjects affected / exposed occurrences (all)	8 / 89 (8.99%) 8	5 / 90 (5.56%) 5	
General disorders and administration site conditions N/A subjects affected / exposed occurrences (all)	22 / 89 (24.72%) 22	17 / 90 (18.89%) 17	
Gastrointestinal disorders N/A subjects affected / exposed occurrences (all)	23 / 89 (25.84%) 23	21 / 90 (23.33%) 21	
Respiratory, thoracic and mediastinal disorders N/A subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 14	13 / 90 (14.44%) 13	
Psychiatric disorders N/A subjects affected / exposed occurrences (all)	13 / 89 (14.61%) 13	9 / 90 (10.00%) 9	
Renal and urinary disorders N/A subjects affected / exposed occurrences (all)	11 / 89 (12.36%) 11	4 / 90 (4.44%) 4	
Infections and infestations N/A subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 17	13 / 90 (14.44%) 13	
Product issues			

N/A subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 9	9 / 90 (10.00%) 9	
Metabolism and nutrition disorders N/A subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 14	10 / 90 (11.11%) 10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33591006