Clinical trial results:
Interleukin-6 Receptor Antibodies for Modulating the Systemic Inflammatory Response after Out-of-Hospital Cardiac Arrest

Summary

EudraCT number	2018-002686-19
Trial protocol	DK
Global end of trial date	31 August 2020

Results information

Result version number	v1 (current)
This version publication date	15 September 2021
First version publication date	15 September 2021

Trial information

Trial identification

Sponsor protocol code	2018-HJEPharma-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03863015
WHO universal trial number (UTN)	-
Other trial identifiers	The IMICA Trial: Acronym

Notes:

Sponsors

Sponsor organisation name	Prof. Hassager, Dept. Cardiology, Rigshospitalet
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Scientific contact	Department of Cardiology, Copenhagen University Hospital Rigshospitalet, christian.hassager@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Out-of-hospital cardiac arrest (OHCA) patients remaining comatose after resuscitation are at high risk of morbidity and mortality due to the post cardiac arrest syndrome (PCAS). Systemic inflammation is a major component of PCAS, and interleukin-6 (IL-6) levels are associated with severity of PCAS. Therefore, tocilizumab, which is an IL-6 receptor antagonist, could potentially dampen inflammation after OHCA.
The objective of the present trial was to determine the efficacy of tocilizumab to reduce systemic inflammation after OHCA of presumed cardiac cause and thereby potentially mitigate organ injury.

The primary endpoint of the study was difference in CRP response between the tocilizumab and placebo group during initial 72 hours.
Secondary endpoints included markers of inflammation, organ injury, neurologic outcome, safety and survival.

For a comprehensive presentation and discussion of trial results please see:
https://doi.org/10.1161/CIRCULATIONAHA.120.053318

Protection of trial subjects:

Participation in the trial did not limit the access to any additional treatments and patients were treated according to standard of care as well (described below). Co-participation in other trials was allowed as well.
Patients with know contraindications to treatment with the study drug (tocilizumab) were excluded during screening. Exclusion criteria included previous allergic reactions to tocilizumab, significant liver impairment, and significant infection as there is a potential immunosuppressive effect of tocilizumab. Further, all patients participating in the trial were treated with prophylactic antibiotics to possibly limit the occurrence of infections during the initial ICU stay.

Background therapy:

In addition to the trial associated treatment, all patients received "standard of care" including sedation, ventilation and targeted temperature management for at least 24 hours, as well as vasopressors/inotropy as needed. Further all patients received prophylactic antibiotics.

Evidence for comparator:

Isotonic saline was chosen as placebo treatment, and no significant effect of this was expected.

Actual start date of recruitment	04 March 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 80

Worldwide total number of subjects	80
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	41
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was completed in 9 months (ahead of schedule)

Pre-assignment

Screening details:

Brief inclusion criteria: Adult comatose patients resuscitated from OHCA of presumed cardiac cause.
We screened 117 patients and randomized 85 patients - tocilizumab: 42, placebo: 43; 5 patients were excluded prior to analysis (tocilizumab: 3; placebo: 2).
Data in this report refer to the resulting modified intention-to-treat population of 80.

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	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Tocilizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	RoActemra, Actemra
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients allocated to the tocilizumab group received a 1-h infusion of 8 mg tocilizumab per kilogram body weight (maximum dose 800 mg, i.e. 40 mL of concentrate); the study drug was suspended in normal saline to a total volume of 100 mL.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	Isotonic saline, NaCl
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients allocated to the placebo arm received a 1-h infusion of 100 mL of normal saline.

Number of subjects in period 1	Tocilizumab	Placebo
Started	39	41
Completed	39	41

Baseline characteristics

Reporting groups	
Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Tocilizumab	Placebo	Total
Number of subjects	39	41	80
Age categorical Units: Subjects			

Age continuous			
Age at time of OHCA			
Units: years			
median	65	60	
inter-quartile range (Q1-Q3)	53 to 73	57 to 70	-
Gender categorical Units: Subjects			
Female	7	7	14
Male	32	34	66

End points

End points reporting groups

Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: C-reactive protein

End point title	C-reactive protein
End point description:	
End point type	Primary
End point timeframe:	
Measured at admission, 24, 48, and 72 hours	

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: mg/L				
median (inter-quartile range (Q1-Q3))				
Admission	2 (1 to 10)	2 (1 to 3)		
24 hours	23 (10 to 45)	123.5 (90 to 169.5)		
48 hours	13 (5 to 32)	202 (151 to 270)		
72 hours	7 (3 to 18)	146.5 (112 to 205)		

Statistical analyses

Statistical analysis title	CRP, mixed model analysis
Statistical analysis description:	
CRP from admission till 72 hours.	
Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001 [2]
Method	Mixed models analysis

Notes:

[1] - Linear mixed model, baseline adjusted.

[2] - P value for the treatment-by-time interaction listed above.

Time specific comparisons of tocilizumab vs placebo:
At 24 hours: p < 0.001
At 48 hours: p < 0.001
At 72 hours: p < 0.001

Secondary: Leukocytes

End point title	Leukocytes

End point description:

End point type	Secondary

End point timeframe:

Measured at admission, 24, 48 and 72 hours

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: 10^9/L				
median (inter-quartile range (Q1-Q3))				
Admission	14.5 (10.5 to 17.9)	18.2 (14.1 to 21)		
24 hours	7.5 (4.8 to 13.5)	12.8 (10.35 to 16.15)		
48 hours	7.3 (5.8 to 12.8)	12 (10.15 to 14.85)		
72 hours	7.7 (5.7 to 10.6)	11.45 (9.6 to 12.6)		

Statistical analyses

Statistical analysis title	Leukocytes, mixed model analysis

Statistical analysis description:

Leukocytes from admission till 72 hours

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0005 [4]
Method	Mixed models analysis

Notes:

[3] - Linear mixed model, baseline adjusted.

[4] - P value for the treatment-by-time interaction listed above.
Time specific comparisons of tocilizumab vs placebo:
At 24 hours: p < 0.001
At 48 hours: p = 0.004
At 72 hours: p = 0.129

Secondary: Troponin T (TnT)

End point title	Troponin T (TnT)

End point description:

End point type	Secondary

End point timeframe:

Measured at admission, 6, 12, 24, 36, 48 and 72 hours.

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: ug/L				
median (inter-quartile range (Q1-Q3))				
Admission	190.5 (102 to 606)	217 (108 to 634)		
6 hours	908 (206 to 2680)	1330 (764 to 3080)		
12 hours	665 (206 to 2550)	1150 (484 to 3420)		
24 hours	435 (169 to 2830)	881.5 (310.5 to 3345)		
36 hours	370.5 (109.5 to 1970)	666 (304 to 2900)		
48 hours	289.5 (113 to 1660)	548 (225 to 2530)		
72 hours	256 (92.5 to 1935)	536 (175 to 1860)		

Statistical analyses

Statistical analysis title	TnT, mixed model analysis

Statistical analysis description:

TnT from admission till 72 hours.

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.0932 [6]
Method	Mixed models analysis

Notes:

[5] - Linear mixed model, baseline adjusted.

[6] - P value for the treatment-by-time interaction listed above.
Time specific comparisons of tocilizumab vs placebo:
At 6 hours: p = 0.002
At 12 hours: p = 0.008
At 24 hours: p = 0.065
At 36 hours: NS
At 48 hours: NS
At 72 hours: NS

Secondary: Creatine kinase myocardial band (CKMB)

End point title	Creatine kinase myocardial band (CKMB)

End point description:

End point type	Secondary

End point timeframe:

Measured at admission, 6, 12, 24, 36, 48 and 72 hours.

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: ug/L				
median (inter-quartile range (Q1-Q3))				
Admission	7.7 (4 to 31.8)	9.8 (7.1 to 31.9)		
6 hours	27.7 (10.2 to 171)	62.75 (30.6 to 185)		
12 hours	30.6 (10.8 to 170)	61.7 (21.6 to 186)		
24 hours	23.4 (8.9 to 116)	44 (18.5 to 131.5)		
36 hours	18.35 (6.95 to 54.85)	25.45 (10.7 to 64.4)		
48 hours	8.85 (4.75 to 25.95)	13.5 (7.6 to 35.4)		
72 hours	5.95 (2.75 to 16.25)	7.8 (3.7 to 11.2)		

Statistical analyses

Statistical analysis title	CKMB, mixed model analysis

Statistical analysis description:

CKMB from admission till 72 hours

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0035 [8]
Method	Mixed models analysis

Notes:

[7] - Linear mixed model, baseline adjusted.

[8] - P value for the treatment-by-time interaction listed above.
Time specific comparisons of tocilizumab vs placebo:
At 6 hours: p < 0.001
At: 12 hours: p = 0.001
At 24 hours: p = 0.050
At 36 hours: NS
At 48 hours: NS
At 72 hour: NS

Secondary: N-terminal pro B-type natriuretic peptide (NT-proBNP)

End point title	N-terminal pro B-type natriuretic peptide (NT-proBNP)

End point description:

End point type	Secondary

End point timeframe:

Measured at admission and 48 hours.

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: pmol/L				
median (inter-quartile range (Q1-Q3))				
Admission	97.6 (27.7 to 427)	44.9 (14.3 to 162)		
48 hours	122.5 (52.85 to 374.5)	179 (88.2 to 491)		

Statistical analyses

Statistical analysis title	NT-proBNP, mixed model analysis

Statistical analysis description:

NT-proBNP from admission till 48 hours.

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0002 [10]
Method	Mixed models analysis

Notes:

[9] - Linear mixed model, baseline adjusted.

[10] - P value for the treatment-by-time interaction listed above.
Time specific comparisons of tocilizumab vs placebo:
At 48 hours: $p < 0.001$

Secondary: Neuron-specific enolase (NSE)

End point title	Neuron-specific enolase (NSE)

End point description:

End point type	Secondary

End point timeframe:

Measured at 48 and 72 hours.

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: ug/L				
median (inter-quartile range (Q1-Q3))				
48 hours	24 (17.6 to 56.8)	20.85 (14.5 to 37)		
72 hours	20 (17.1 to 30)	17 (12.8 to 22.4)		

Statistical analyses

Statistical analysis title	NSE, mixed model
Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.27 [12]
Method	Mixed models analysis

Notes:

[11] - Linear mixed model.

[12] - P value for the treatment-by-time interaction listed above.
Time specific comparisons of tocilizumab vs placebo:
At 48 hours: p = 0.22
At 72 hours: p = 0.39

Secondary: Cerebral Performance Category (CPC) after 180 days

End point title	Cerebral Performance Category (CPC) after 180 days

End point description:

A score ≥3 indicate a poor neurologic outcome (incl. death)

End point type	Secondary

End point timeframe:

180 days after Out-of-hospital cardiac arrest

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: Score				
≥3	15	15		

Statistical analyses

Statistical analysis title	CPC after 180 days

Statistical analysis description:

Comparing the frequency of a poor neurologic outcome in the two groups

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Secondary: Modified Rankin Scale (mRS) after 180 days

End point title	Modified Rankin Scale (mRS) after 180 days

End point description:

A score ≥4 indicate a poor neurologic outcome (incl. death)

End point type	Secondary

End point timeframe:

180 days after Out-of-hospital cardiac arrest

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: Score				
≥4	16	14		

Statistical analyses

Statistical analysis title	mRS after 180 days

Statistical analysis description:

Comparing the frequency of a poor neurologic outcome in the two groups

Comparison groups	Tocilizumab v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.65
Method	Fisher exact

Secondary: Mortality after 180 days

End point title	Mortality after 180 days

End point description:

End point type	Secondary

End point timeframe:

180 days after Out-of-hospital cardiac arrest

End point values	Tocilizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: No.				
Deaths after 180 days	14	14		

Statistical analyses

Statistical analysis title	Mortality after 180 days
Comparison groups	Placebo v Tocilizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization till 6 months after

Assessment type	Systematic

Dictionary used

Dictionary name	Study protocol
Dictionary version	1.91

Reporting groups

Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Tocilizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 39 (51.28%)	21 / 41 (51.22%)	
number of deaths (all causes)	14	14	
number of deaths resulting from adverse events	14	14	
Cardiac disorders			
Arrhythmia	Additional description: An AE of arrhythmia that fulfilled the criteria for being classifies as a SAE.		
subjects affected / exposed	3 / 39 (7.69%)	4 / 41 (9.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
General disorders and administration site conditions			
Bleeding	Additional description: An AE of bleeding that fulfilled the criteria for being a SAE.		
subjects affected / exposed	1 / 39 (2.56%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Other	Additional description: An AE of "other" that fulfilled the criteria for being a SAE. This category also includes deaths as a result of withdrawal of life sustaining therapy due to irreversible brain injury after the cardiac arrest.		
subjects affected / exposed	17 / 39 (43.59%)	17 / 41 (41.46%)	
occurrences causally related to treatment / all	0 / 20	0 / 17	
deaths causally related to treatment / all	0 / 14	0 / 10	
Infections and infestations			
Infection	Additional description: An AE of infection that fulfilled the criteria for being a SAE.		

	By definition all infections in the trial was classified as "possibly" related to the intervention.		
subjects affected / exposed	2 / 39 (5.13%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Tocilizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)	40 / 41 (97.56%)	
Cardiac disorders			
Arrhythmia	Additional description: Defined as the occurrence of VF, VT, AF, need for pacing, or circulatory collapse		
subjects affected / exposed	7 / 39 (17.95%)	16 / 41 (39.02%)	
occurrences (all)	8	19	
Nervous system disorders			
Seizures	Additional description: Defined as the occurrence of seizures, including tonic-clonic, myoclonic, status epilepticus		
subjects affected / exposed	9 / 39 (23.08%)	8 / 41 (19.51%)	
occurrences (all)	9	8	
General disorders and administration site conditions			
Bleeding	Additional description: Defined as the occurrence of bleeding, either diagnosed in-hospital or requiring in-hospital treatment.		
subjects affected / exposed	11 / 39 (28.21%)	6 / 41 (14.63%)	
occurrences (all)	13	6	
Other	Additional description: Other adverse events potentially related to the intervention.		
subjects affected / exposed	8 / 39 (20.51%)	7 / 41 (17.07%)	
occurrences (all)	10	7	
Renal and urinary disorders			
Dialysis	Additional description: Temporary use of dialysis/renal replacement therapy during ICU stay		
subjects affected / exposed	10 / 39 (25.64%)	2 / 41 (4.88%)	
occurrences (all)	10	2	
Infections and infestations			
Infection	Additional description: Defined as the occurrence infections either diagnosed in-hospital or requiring in-hospital treatment. By definition all infections occurring in the trial were classified as being at least "possibly" related to the intervention.		
subjects affected / exposed	4 / 39 (10.26%)	9 / 41 (21.95%)	
occurrences (all)	5	11	
Metabolism and nutrition disorders			

Electrolyte imbalance	Additional description: Defined as a serum K <3 or >5		
subjects affected / exposed	23 / 39 (58.97%)	20 / 41 (48.78%)	
occurrences (all)	29	22	
Metabolic disorder	Additional description: Defined as the occurrence of a serum glucose <3mM, or >10mM for >4 hours		
subjects affected / exposed	18 / 39 (46.15%)	27 / 41 (65.85%)	
occurrences (all)	20	28	

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/33081828

http://www.ncbi.nlm.nih.gov/pubmed/33745292