Clinical trial results:
Efficacy and safety of ANAkinra during Adult « COVID-19 » with Aggravating respiratory symptoms: a multicenter open-label controlled randomized trial

Summary

EudraCT number	2020-001734-36
Trial protocol	FR
Global end of trial date	03 November 2020

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	DR200111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04364009
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU Tours
Sponsor organisation address	Boulevard Tonnellé, Tours, France, 37044 cedex 9
Public contact	Clinical Research Associate, CHRU de TOURS, +33 247474665, e.mousset@chu-tours.fr
Scientific contact	Coordinating investigator, CHRU de TOURS, +33 247473715, alexandra.audemardverger@univ-tours.fr

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 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 October 2020
Global end of trial reached?	Yes
Global end of trial date	03 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the ANACONDA-COVID-19 trial is to assess the efficacy of Anakinra + optimized Standard of Care (oSOC) as compared to oSOC alone on the condition of patients with COVID-19 infection and worsening respiratory symptoms. Success defined as patient alive and free of invasive mechanical ventilation (IMV) and free of Extracorporeal Membrane Oxygenation (ECMO) at Day 14.

Protection of trial subjects:

An interim analysis for efficacy analysis was planned after the primary outcome has been obtained for the first 120 patients and for safety concerns each 60 patients.

Background therapy: -

Evidence for comparator:

Analgesic treatment, transfusion of blood products, electrolyte and glucose infusions, IV, parenteral nutrition, inotropic support, antibiotics, anti-fungal and anti-viral treatments, ultrafiltration or hemodialysis, as well as general supportive care were allowed. Other therapy considered necessary for the patient’s welfare could be given at the discretion of the Investigator. Due to the lack of sufficient scientific evidence hydroxychloroquine chloroquine and antiretrovirals were not recommended but not prohibited because clinical trials were ongoing. Regarding corticosteroid therapy, due to a potential effectiveness, and the absence of a clearly negative study and a potential synergy with Anakinra, the clinician taking the choice of whether or not to initiate corticosteroid therapy support the patient. A standardized corticosteroid regimen was proposed. Randomization was stratified on the presence or absence of corticosteroid therapy and don’t lead to bias in our study

Actual start date of recruitment	27 April 2020
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	France: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	20
From 65 to 84 years	41
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The recruitment started on 27th avril 2020.

Pre-assignment

Screening details:

Patients were screened by 45 COVID referent centers. All patients with a positive COVID-19 diagnosis were considered for inclusions. Inclusion and exclusion criteria were first checked during a routine/daily medical visit. The duration of screening period should not exceed 24h.

Period 1

Period 1 title	Inclusion
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anakinra plus optimized standard of care

Arm description:

The experimental group received Anakinra plus optimized standard of care. The patients received intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days.

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

Dosage and administration details:

The patients received Intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) during 3 days. Then, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours) during 7 days. The total duration of Anakinra is 10 Days.

Arm title	optimized standard of care

Arm description:

The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.

Arm type	Usual care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Anakinra plus optimized standard of care	optimized standard of care
Started	37	34
Completed	30	34
Not completed	7	0
Adverse event, serious fatal	6	-

Consent withdrawn by subject	1	-

Period 2

Period 2 title	Day 14
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Anakinra+SOC

Arm description:

The experimental group received Anakinra plus optimized Standard of Care.
The patients received Intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days

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

Dosage and administration details:

The patients received Intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) during 3 days. Then, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours) during 7 days. The total duration of Anakinra is 10 Days.

Arm title	Optimized Standard of Care

Arm description:

The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.

Arm type	Usual care

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Anakinra+SOC	Optimized Standard of Care
Started	30	34
Completed	27	28
Not completed	3	6
Adverse event, serious fatal	3	5
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Anakinra plus optimized standard of care
Reporting group description:	
The experimental group received Anakinra plus optimized standard of care. The patients received intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days.	
Reporting group title	optimized standard of care
Reporting group description:	
The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.	

Reporting group values	Anakinra plus optimized standard of care	optimized standard of care	Total
Number of subjects	37	34	71
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	10	20
From 65-84 years	21	20	41
85 years and over	6	4	10
Age continuous Units: years			
arithmetic mean	71	70	
standard deviation	± 14	± 14	-
Gender categorical Units: Subjects			
Female	9	10	19
Male	28	24	52

End points

End points reporting groups

Reporting group title	Anakinra plus optimized standard of care

Reporting group description:

The experimental group received Anakinra plus optimized standard of care. The patients received intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days.

Reporting group title	optimized standard of care

Reporting group description:

The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.

Reporting group title	Anakinra+SOC

Reporting group description:

The experimental group received Anakinra plus optimized Standard of Care.
The patients received Intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days

Reporting group title	Optimized Standard of Care

Reporting group description:

The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.

Primary: Treatment success at day 14

End point title	Treatment success at day 14

End point description:

End point type	Primary

End point timeframe:

At day 14

End point values	Anakinra plus optimized standard of care	optimized standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	34		
Units: Percentage	26	31		

Attachments (see zip file)	Flow_chart.jpg

Statistical analyses

Statistical analysis title	Risk difference
Comparison groups	optimized standard of care v Anakinra plus optimized standard of care
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.2
upper limit	-1.8

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Real time reporting from the day that written informed consent is provided until 28 days after the inclusion

Adverse event reporting additional description:

This initial reporting must be provided in writing and should quickly be followed by a detailed written supplementary report

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Anakinra plus optimized standard of care

Reporting group description:

The experimental group received Anakinra plus optimized Standard of Care. The patients received Intraveinous injection (IV) of Anakinra 400mg/day (100mg IV every 6 hours) at Day 1, 2 and 3. From Day 4 to Day 10, the patient received IV injection of Anakinra 200mg/day (100mg every 12 hours). The total duration of Anakinra was 10 Days.

Reporting group title	optimized standard of care

Reporting group description:

The control group received optimized standard of care alone, including all treatments authorized for COVID-19 by the French Health Ministry at inclusion and during the follow-up.

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 list of adverse events is not available.

Serious adverse events	Anakinra plus optimized standard of care	optimized standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 37 (51.35%)	18 / 34 (52.94%)	
number of deaths (all causes)	9	5	
number of deaths resulting from adverse events	8	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer	Additional description: Progression of prostate cancer		
subjects affected / exposed	0 / 37 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Wrong dose	Additional description: delay in adaptation of anakinra following clearance <30		
subjects affected / exposed	2 / 37 (5.41%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Vasoplegia syndrome			
subjects affected / exposed	1 / 37 (2.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 37 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death	Additional description: sudden death		
subjects affected / exposed	1 / 37 (2.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal disorders			
Haemorrhage	Additional description: Haemorrhage of digestive tract		
subjects affected / exposed	0 / 37 (0.00%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic enzyme abnormal	Additional description: Hepatic cytolysis		
subjects affected / exposed	1 / 37 (2.70%)	2 / 34 (5.88%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 37 (5.41%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Acute respiratory failure	Additional description: Acute respiratory decompensation		
subjects affected / exposed	12 / 37 (32.43%)	12 / 34 (35.29%)	
occurrences causally related to treatment / all	0 / 12	0 / 12	
deaths causally related to treatment / all	0 / 5	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 37 (2.70%)	1 / 34 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 37 (2.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure	Additional description: Renal failure aggravated		
subjects affected / exposed	1 / 37 (2.70%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Anakinra plus optimized standard of care	optimized standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 34 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2020	- Addition of 4 centers - Protocole's modification : At V3, for the group SOC alone, this visit will be performed at hospital or by phone if the patient is discharged from the hospital in order to avoid hospital saturation
25 May 2020	- Restart of inclusions after the declaration of a new-fact - Modification of DSMB meeting - Addition of 4 centers
18 June 2020	- Prolongation of period recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 May 2020	Following the occurrence of serious adverse events reported for patients included in the ANACONDA-COVID-19 study and the difference of this occurrence between the two group of randomisation, the CHRU of Tours, promoter of the study, in agreement with the coordinating investigator, decided to refer the matter to the Independent Monitoring Committee of the study. As a safety measure, pending their opinion and recommendations, it was decided to suspend the inclusions.	06 July 2020

Notes:

Limitations and caveats

None reported