Clinical trial results:
Pre-emptive tocilizumab in hypoxic COVID-19 patients, a prospective randomized trial

Summary

EudraCT number	2020-001375-32
Trial protocol	NL
Global end of trial date	19 February 2021

Results information

Result version number	v1 (current)
This version publication date	25 October 2022
First version publication date	25 October 2022

Trial information

Trial identification

Sponsor protocol code	PreToVid

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UMCG
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands, 9713 GZ
Public contact	Principal Investigator, UMCG, a.rutgers@umcg.nl
Scientific contact	Principal Investigator, UMCG, a.rutgers@umcg.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	19 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2021
Global end of trial reached?	Yes
Global end of trial date	19 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess in a randomized comparison the effect of pre-emptive Tocilizumab in patients with hypoxia due to COVID-19 on 30-day mortality (from randomization)

Protection of trial subjects:

There are no specific antidotes. Apheresis may be performed to dialyze tocilizumab.
After treatment with tocilizumab toxicity has to be carefully examined and evaluated. During the clinical phase a daily assessment of toxicities will be performed. After discharge patients will be followed until 3 months after randomization. In the outpatient setting an assessment of toxicities will be performed. The toxicity assessment includes the following:
• Complete history of symptoms and complaints
• Complete physical examination
• Laboratory examination of hemogram, ALT/AST, bilirubin, Creatinin, LDH; other parameters as clinically indicated
• Chest X-ray when clinically indicated
• Electrocardiography when indicated

Background therapy:

There is no other treatment for COVID except for oxygen administration

Evidence for comparator:

As high IL-6 levels are strongly associated with shorter survival in Covid-19 and IL-6 signalling can be efficiently blocked by the IL-6 inhibitor tocilizumab, we hypothesized that early (pre-emptive) intervention with tocilizumab might beneficially alter the course of Covid-19 CRS. We postulated that tocilizumab might reduce progression to hypoxemic respiratory failure and death, reduce the risk of admission to the intensive care unit (ICU) and decrease the duration of ICU and hospital stay. To this end we designed and carried out an investigator-initiated trial, the 'Pre-emptive Tocilizumab for hospitalized Covid-19 patients' (PreToVid) trial. This prospective randomized trial compared standard of care with or without tocilizumab in Covid-19 patients admitted to hospital and in need of oxygen supplementation.

Actual start date of recruitment	06 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	Netherlands: 354
Worldwide total number of subjects	354
EEA total number of subjects	354

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)	153
From 65 to 84 years	184
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

The first patient with Covid-19 in The Netherlands was diagnosed on February 27, 2020. The first patient in this trial was included on April 6, 2020, and the final patient was included on January 12, 2021. A total of 354 patients were randomized and all were included in the intention-to-treat population.

Pre-assignment

Screening details:

18 years or older, capable of providing informed consent and had confirmed SARS-CoV-2 infection. Additionally, patients were admitted to a ward and have signs compatible with hyperinflammation: need for supplemental oxygen or ferritin >2000ug/l or a doubling of serum ferritin in 20-48 hrs

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

na

Arms

Are arms mutually exclusive?	Yes
Arm title	SOC + tocilizumab

Arm description:

standard of care plus tocilizumab

Arm type	Experimental
Investigational medicinal product name	tocilizumab
Investigational medicinal product code	L04AC07
Other name	Roactemra
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Patients in this study are treated with intravenous tociluzumab: 8 mg/kg (maximum dose 800 mg), which can
be repeated at the same dose after 8 hours if the hypoxia has not improved. This is the approved dose for cytokine release syndrome.

Arm title	Standard of Care (SOC)

Arm description:

standard of care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	SOC + tocilizumab	Standard of Care (SOC)
Started	174	180
30-day mortality	170	177
Completed	170	177
Not completed	4	3

Consent withdrawn by subject	4	3

Baseline characteristics

Reporting groups	
Reporting group title	SOC + tocilizumab
Reporting group description: standard of care plus tocilizumab	
Reporting group title	Standard of Care (SOC)
Reporting group description: standard of care	

Reporting group values	SOC + tocilizumab	Standard of Care (SOC)	Total
Number of subjects	174	180	354
Age categorical Units: Subjects			
18-65	81	89	170
>65	93	91	184
Age continuous Units: years			
median	67	66	
inter-quartile range (Q1-Q3)	60 to 74	56 to 75	-
Gender categorical Units: Subjects			
Female	57	59	116
Male	117	121	238

End points

End points reporting groups	
Reporting group title	SOC + tocilizumab
Reporting group description: standard of care plus tocilizumab	
Reporting group title	Standard of Care (SOC)
Reporting group description: standard of care	

Primary: 30-day survival	
End point title	30-day survival
End point description:	
End point type	Primary
End point timeframe: 30 days after inclusion	

End point values	SOC + tocilizumab	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	180		
Units: 347				
alive at 30 days	153	146		
death at 30 days	21	34		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: The primary analysis–the difference in 30-day mortality between the two arms–entailed Cox regression analysis with adjustment for only the stratification factor ICU-eligibility	
Comparison groups	SOC + tocilizumab v Standard of Care (SOC)
Number of subjects included in analysis	354
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.1 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	90 %
sides	2-sided

Notes:

[1] - The 0.10 significance level was chosen because of the phase II design, in which a p-value below 0.10 would indicate that further investigation for efficacy would be warranted.

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: until 30 days after randomization	
Adverse event reporting additional description: AEs of CTCAE grade ≥ 4 will be reported	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	SOC + tocilizumab

Reporting group description:

The patients in this group received standard of care with tocilizumab.
AEs of CTCAE grade ≥ 4 are reported from the first study-related procedure until 30 days following the last dose of tocilizumab.

Reporting group title	standard of care

Reporting group description:

The patients in this group received standard of care, no tocilizumab.
AEs of CTCAE grade ≥ 4 are reported from the first study-related procedure until 30 days following the last dose of tocilizumab. Adverse events grade of the standard arm are reported until 30 days after randomization.

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: only SAEs are reported, reporting of non serious AEs was not requested

Serious adverse events	SOC + tocilizumab	standard of care	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 174 (25.86%)	53 / 180 (29.44%)	
number of deaths (all causes)	21	34	
number of deaths resulting from adverse events	9	9	
Blood and lymphatic system disorders			
thromboembolic event			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 174 (4.60%)	4 / 180 (2.22%)	
occurrences causally related to treatment / all	0 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 174 (1.15%)	5 / 180 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Bacteraemia			

alternative assessment type: Systematic			
subjects affected / exposed	3 / 174 (1.72%)	4 / 180 (2.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Immune system disorders			
Worsening of disease	Additional description: patients got to ICU or dead due to the COVID progression		
alternative assessment type: Systematic			
subjects affected / exposed	32 / 174 (18.39%)	40 / 180 (22.22%)	
occurrences causally related to treatment / all	0 / 32	0 / 40	
deaths causally related to treatment / all	0 / 18	0 / 28	

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

Non-serious adverse events	SOC + tocilizumab	standard of care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 174 (0.00%)	0 / 180 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2020	Adding 11 hospitals for participating in the study
17 April 2020	Adding another two hospital for participating in the study
24 April 2020	Adding three hospitals for participating in the study
08 May 2020	Adding another hospitals for participating in the study and changing a PI for one of the participating hospitals
19 June 2020	adding secondary endpoint: To asses in a randomized comparison quality of life and pulmonary function after 3 months (after randomization) (Synopsis; 6.2, 13.2) adding risk classification: Negligible (Synopsis) protocol changed for multicenter study, clarification of assessments and other text. Patient information updated for way of sampling, questionnaires and sharing SAEs with sponsor of tocilizumab.
24 September 2020	Change in second meeting DSMB adding stratification for dexamethason and remdesivir. Update of DSMB charter

Notes:

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/34228774

http://www.ncbi.nlm.nih.gov/pubmed/35960720