



Clinical trial results:

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

Summary

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|--------------------------|------------------|
| 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 tocilizumab: 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

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|-----------------------|-------------------|
| Reporting group title | SOC + tocilizumab |
|-----------------------|-------------------|

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|---|
| Reporting group description: standard of care plus tocilizumab |
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| | |
|-----------------------|------------------------|
| 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

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|-----------------|-------|
| 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>