# Clinical trial results:
# A multicenter, randomized, active controlled, open label, platform trial on the efficacy and safety of experimental therapeutics for patients with COVID-19 (caused by infection with severe acute respiratory syndrome coronavirus-2)

## ACOVACT (Austrian CoronaVirus Adaptive Clinical Trial)

### Summary

| | |
|---|---|
| EudraCT number | 2020-001302-30 |
| Trial protocol | AT |
| Global end of trial date | 03 November 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 November 2023 |
| First version publication date | 19 November 2023 |
| Summary attachment (see zip file) | Adverse Events (ACOVACT_Adverse_Events.pdf) |

### Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ACOVACT |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Medical University of Vienna |
| Sponsor organisation address | Währinger Gürtel 18-20, Vienn, Austria, 1090 |
| Public contact | Sponsor, Medical University of Vienna, Department of Clinical Pharmacology, klin-pharmakologie@meduniwien.ac.at |
| Scientific contact | Sponsor, Medical University of Vienna, Department of Clinical Pharmacology, klin-pharmakologie@meduniwien.ac.at |

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 | 09 February 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 February 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 November 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the efficacy of various experimental therapeutics for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); for efficacy assessment an ordinal scale for clinical severity assessment as proposed by the World Health Organization was used:
Time to sustained improvement of one category from admission.

Protection of trial subjects:

For "antiviral" treatment arms and sub-studies only hospitalized patients were included and intake of medication was intensly controlled.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 April 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 345 |
| Worldwide total number of subjects | 345 |
| EEA total number of subjects | 345 |

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) | 225 |
| From 65 to 84 years | 112 |
| 85 years and over | 8 |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were selected per study site from the pool of admitted patients. No extra recruitment strategies were necessary.

### Pre-assignment

Screening details:

During the screening procedure the patients' eligibility for each trial arm was checked. The main prerequisite was a laboratory or radiologically proven infection with SARS-CoV-2.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Main Study |

Arm description:

Main "antiviral therapy" study:
Reporting group 1: Resochin/Quensyl
Reporting group 2: Kaletra
Reporting group 3: Veklury
Reporting group 4: Standard of care (SOC) ("control arm" of the study)

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Quensyl |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200mg 2-0-2 Maintenance dose: 200 mg 1-0-1

| | |
|---|---|
| Investigational medicinal product name | Kaletra |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Kaletra low-dose: Initial and maintenance dose: 200 mg/50 mg 2-0-2
Kaletra high-dose: Initial dose: 200 mg/50 mg 4-0-4, maintenance dose: 200mg/50mg 3-0-3

| | |
|---|---|
| Investigational medicinal product name | Veklury |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Initial dose: 200mg/day
Maintenance dose: 100mg/day

| | |
|---|---|
| **Arm title** | Substudy A |

Arm description:

Subjects received Xarelto versus standard of care

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Xarelto |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Initial dose: 10 mg 1/2-0-1/2
Maintenance dose: down-titration allowed in case of high anti-FXa activity before the next dose

| | |
|---|---|
| **Arm title** | Substudy B- Cohort 1 |

Arm description:

- Stay on any RAS blockade: patients with previously known and treated hypertension (treatment according to standard of care).
- Switch to non-RAS blocking agent: switch of patients with previously known and treated hypertension to non-RAS blocking agents (treatment according to standard of care, e.g. nitrendipine, amlodipine or doxazosin)

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | Substudy B- Cohort 2 |

Arm description:

- Treatment with RAS blocking agent: treatment of patients with blood pressure >130/85mmHg in two consecutive measurements with RAS blocking agent candesartan (Blopress)
- Non-RAS blocking agents: treatment according to standard of care, e.g. with nitrendipine, amlodipine or doxazosin, or no treatment, if blood pressure <140/90mmHg.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Blopress |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Initial dose: candesartan 8 mg 1-0-0;
Maintenance dose: Up-titration to normotension

| | |
|---|---|
| **Arm title** | Substudy C - Asunercept |

Arm description:

- Asunercept randomized against standard of care (25 mg, 100 mg or 400 mg according to the respective randomized sub-arm)

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Asunercept |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Initial dose: 25 mg, 100 mg or 400 mg once a week according to the respective randomized sub-arm.
Maintenance dose: same as first dosage.

| | |
|---|---|
| **Arm title** | Substudy C - Pentaglobin |

Arm description:

- Pentaglobin randomized against standard of care

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Pentaglobin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Continuous i.v. application of a total dose of 7ml/kg/day
Infusion over 12h

| **Number of subjects in period 1** | Main Study | Substudy A | Substudy B- Cohort 1 |
|---|---|---|---|
| Started | 224 | 145 | 60 |
| Completed | 214 | 140 | 59 |
| Not completed | 10 | 5 | 1 |
| Own Request | 3 | 2 | - |
| screening failure | 3 | 1 | - |
| dropout | 4 | 2 | 1 |

| **Number of subjects in period 1** | Substudy B- Cohort 2 | Substudy C - Asunercept | Substudy C - Pentaglobin |
|---|---|---|---|
| Started | 8 | 102 | 34 |
| Completed | 7 | 99 | 32 |
| Not completed | 1 | 3 | 2 |
| Own Request | - | 3 | - |
| screening failure | 1 | - | 1 |
| dropout | - | - | 1 |

## Baseline characteristics

| Reporting groups[1] | |
|---|---|
| Reporting group title | Main Study |
| Reporting group description: | |
| Main "antiviral therapy" study:<br>Reporting group 1: Resochin/Quensyl<br>Reporting group 2: Kaletra<br>Reporting group 3: Veklury<br>Reporting group 4: Standard of care (SOC) ("control arm" of the study) | |
| Reporting group title | Substudy A |
| Reporting group description: | |
| Subjects received Xarelto versus standard of care | |
| Reporting group title | Substudy B- Cohort 1 |
| Reporting group description: | |
| • Stay on any RAS blockade: patients with previously known and treated hypertension (treatment according to standard of care).<br>• Switch to non-RAS blocking agent: switch of patients with previously known and treated hypertension to non-RAS blocking agents (treatment according to standard of care, e.g. nitrendipine, amlodipine or doxazosin) | |
| Reporting group title | Substudy B- Cohort 2 |
| Reporting group description: | |
| • Treatment with RAS blocking agent: treatment of patients with blood pressure >130/85mmHg in two consecutive measurements with RAS blocking agent candesartan (Blopress)<br>• Non-RAS blocking agents: treatment according to standard of care, e.g. with nitrendipine, amlodipine or doxazosin, or no treatment, if blood pressure <140/90mmHg. | |
| Reporting group title | Substudy C - Asunercept |
| Reporting group description: | |
| • Asunercept randomized against standard of care (25 mg, 100 mg or 400 mg according to the respective randomized sub-arm) | |
| Reporting group title | Substudy C - Pentaglobin |
| Reporting group description: | |
| • Pentaglobin randomized against standard of care | |

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Arms were not mutually exclusive. Total number of enrolled subjects was 345.

| Reporting group values | Main Study | Substudy A | Substudy B- Cohort 1 |
|---|---|---|---|
| Number of subjects | 224 | 145 | 60 |
| Age categorical<br>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) | 144 | 102 | 28 |
| From 65-84 years | 75 | 38 | 32 |
| 85 years and over | 5 | 5 | 0 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 72 | 45 | 23 |
| Male | 152 | 100 | 37 |

| **Reporting group values** | Substudy B- Cohort 2 | Substudy C - Asunercept | Substudy C - Pentaglobin |
|---|---|---|---|
| Number of subjects | 8 | 102 | 34 |
| Age categorical<br>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) | 7 | 63 | 30 |
| From 65-84 years | 1 | 36 | 4 |
| 85 years and over | 0 | 3 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 29 | 8 |
| Male | 8 | 73 | 26 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 345 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 225 | | |
| From 65-84 years | 112 | | |
| 85 years and over | 8 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 104 | | |
| Male | 241 | | |

## Subject analysis sets

| | |
|---|---|
| Subject analysis set title | Main study: Quensyl |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Quensyl.

| Subject analysis set title | Main study: Kaletra |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Kaletra

| Subject analysis set title | Main study: Veklury |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Veklury.

| Subject analysis set title | Main study: Standard of care |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving standard of care.

| Subject analysis set title | Substudy A: Xarelto |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Xarelto in substudy A.

| Subject analysis set title | Substudy A: standard of care |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving standard of care in substudy A.

| Subject analysis set title | Substudy B-Cohort 1 Stay on any RAS |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with previously known and treated hypertension (treatment according to standard of care).

| Subject analysis set title | Substudy B-Cohort 1 Switch to non RAS |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with previously known and treated hypertension who switch to non-RAS blocking agents (treatment according to standard of care, e.g. nitrendipine, amlodipine or doxazosin)

| Subject analysis set title | Substudy B-Cohort 2 Blopress |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with blood pressure >130/85mmHg in two consecutive measurements with treatment of RAS blocking agent candesartan (Blopress)

| Subject analysis set title | Substudy B-Cohort 2 non RAS |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects with treatment according to standard of care, e.g. with nitrendipine, amlodipine or doxazosin, or no treatment, if blood pressure <140/90mmHg.

| Subject analysis set title | Substudy C- Asunercept high dose |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical

performance scale, which were measured daily till day 29 for subject receiving Asunercept high dose (400mg).

| Subject analysis set title | Substudy C- Asunercept intermediate dose |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving for Asunercept intermedian dose (100mg).

| Subject analysis set title | Substudy C- Asunercept low dose |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Asunercept low dose (25mg).

| Subject analysis set title | Substudy C Asunercept standard of care |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving standard of care in substudy C Asunercept

| Subject analysis set title | Substudy C Pentaglobin |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Pentaglobin

| Subject analysis set title | Substudy C Pentaglobin standard of care |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving standard of care in substudy C Pentaglobin

| **Reporting group values** | Main study: Quensyl | Main study: Kaletra | Main study: Veklury |
|---|---|---|---|
| Number of subjects | 11 | 101 | 2 |
| Age categorical<br>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) | 8 | 60 | 1 |
| From 65-84 years | 3 | 40 | 1 |
| 85 years and over | 0 | 1 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 33 | 1 |
| Male | 9 | 68 | 1 |

| **Reporting group values** | Main study: Standard of care | Substudy A: Xarelto | Substudy A: standard of care |
|---|---|---|---|
| Number of subjects | 105 | 70 | 73 |

| | | | |
|---|---|---|---|
| Age categorical<br>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) | 72 | 49 | 52 |
| From 65-84 years | 30 | 17 | 21 |
| 85 years and over | 3 | 4 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 34 | 25 | 19 |
| Male | 71 | 45 | 54 |

| **Reporting group values** | Substudy B-Cohort 1 Stay on any RAS | Substudy B-Cohort 1 Switch to non RAS | Substudy B-Cohort 2 Blopress |
|---|---|---|---|
| Number of subjects | 32 | 28 | 3 |
| Age categorical<br>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) | 13 | 15 | 3 |
| From 65-84 years | 19 | 13 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 9 | 14 | 0 |
| Male | 23 | 14 | 3 |

| **Reporting group values** | Substudy B-Cohort 2 non RAS | Substudy C-Asunercept high dose | Substudy C-Asunercept intermediate dose |
|---|---|---|---|
| Number of subjects | 4 | 25 | 23 |
| Age categorical<br>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) | 3 | 14 | 14 |
| From 65-84 years | 1 | 8 | 9 |

| | | | |
|---|---|---|---|
| 85 years and over | 0 | 3 | 0 |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 5 | 6 |
| Male | 4 | 20 | 17 |

| **Reporting group values** | Substudy C-Asunercept low dose | Substudy C Asunercept standard of care | Substudy C Pentaglobin |
|---|---|---|---|
| Number of subjects | 26 | 25 | 17 |
| Age categorical<br>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) | 17 | 16 | 15 |
| From 65-84 years | 9 | 9 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 5 | 13 | 4 |
| Male | 21 | 12 | 13 |

| **Reporting group values** | Substudy C Pentaglobin standard of care | | |
|---|---|---|---|
| Number of subjects | 16 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 14 | | |
| From 65-84 years | 2 | | |
| 85 years and over | 0 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | | |
| Male | 12 | | |

## End points

### End points reporting groups

| Reporting group title | Main Study |
|---|---|

Reporting group description:

Main "antiviral therapy" study:
Reporting group 1: Resochin/Quensyl
Reporting group 2: Kaletra
Reporting group 3: Veklury
Reporting group 4: Standard of care (SOC) ("control arm" of the study)

| Reporting group title | Substudy A |
|---|---|

Reporting group description:

Subjects received Xarelto versus standard of care

| Reporting group title | Substudy B- Cohort 1 |
|---|---|

Reporting group description:

- Stay on any RAS blockade: patients with previously known and treated hypertension (treatment according to standard of care).
- Switch to non-RAS blocking agent: switch of patients with previously known and treated hypertension to non-RAS blocking agents (treatment according to standard of care, e.g. nitrendipine, amlodipine or doxazosin)

| Reporting group title | Substudy B- Cohort 2 |
|---|---|

Reporting group description:

- Treatment with RAS blocking agent: treatment of patients with blood pressure >130/85mmHg in two consecutive measurements with RAS blocking agent candesartan (Blopress)
- Non-RAS blocking agents: treatment according to standard of care, e.g. with nitrendipine, amlodipine or doxazosin, or no treatment, if blood pressure <140/90mmHg.

| Reporting group title | Substudy C - Asunercept |
|---|---|

Reporting group description:

- Asunercept randomized against standard of care (25 mg, 100 mg or 400 mg according to the respective randomized sub-arm)

| Reporting group title | Substudy C - Pentaglobin |
|---|---|

Reporting group description:

- Pentaglobin randomized against standard of care

| Subject analysis set title | Main study: Quensyl |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Quensyl.

| Subject analysis set title | Main study: Kaletra |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Kaletra

| Subject analysis set title | Main study: Veklury |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Veklury.

| Subject analysis set title | Main study: Standard of care |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving standard of care.

| Subject analysis set title | Substudy A: Xarelto |
|---|---|

| | |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving Xarelto in substudy A.

| | |
|---|---|
| Subject analysis set title | Substudy A: standard of care |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects receiving standard of care in substudy A.

| | |
|---|---|
| Subject analysis set title | Substudy B-Cohort 1 Stay on any RAS |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with previously known and treated hypertension (treatment according to standard of care).

| | |
|---|---|
| Subject analysis set title | Substudy B-Cohort 1 Switch to non RAS |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with previously known and treated hypertension who switch to non-RAS blocking agents (treatment according to standard of care, e.g. nitrendipine, amlodipine or doxazosin)

| | |
|---|---|
| Subject analysis set title | Substudy B-Cohort 2 Blopress |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for patients with blood pressure >130/85mmHg in two consecutive measurements with  treatment of RAS blocking agent candesartan (Blopress)

| | |
|---|---|
| Subject analysis set title | Substudy B-Cohort 2 non RAS |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subjects with treatment according to standard of care, e.g. with nitrendipine, amlodipine or doxazosin, or no treatment, if blood pressure <140/90mmHg.

| | |
|---|---|
| Subject analysis set title | Substudy C- Asunercept high dose |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Asunercept high dose (400mg).

| | |
|---|---|
| Subject analysis set title | Substudy C- Asunercept intermediate dose |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving for Asunercept intermedian dose (100mg).

| | |
|---|---|
| Subject analysis set title | Substudy C- Asunercept low dose |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Asunercept low dose (25mg).

| | |
|---|---|
| Subject analysis set title | Substudy C Asunercept standard of care |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving standard of care in substudy C Asunercept

| | |
|---|---|
| Subject analysis set title | Substudy C Pentaglobin |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving Pentaglobin

| | |
|---|---|
| Subject analysis set title | Substudy C Pentaglobin standard of care |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Time to sustained improvement (i.e. >48h) of one category from baseline in the 7-point clinical performance scale, which were measured daily till day 29 for subject receiving standard of care in substudy C Pentaglobin

## Primary: Primary Endpoint Kaletra versus standard of care

| | |
|---|---|
| End point title | Primary Endpoint Kaletra versus standard of care |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

from day 1 to day 29

| End point values | Main study: Kaletra | Main study: Standard of care | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 101 | 105 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 11 (7 to 21) | 9 (6 to 12) | | |

### Statistical analyses

| Statistical analysis title | Analysis primary endpoint Kaletra versus SOC |
|---|---|
| Comparison groups | Main study: Kaletra v Main study: Standard of care |
| Number of subjects included in analysis | 206 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Logrank |

## Primary: Primary endpoint substudy A

| | |
|---|---|
| End point title | Primary endpoint substudy A |

End point description:

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Day 1 to day 29 | |

| **End point values** | Substudy A: Xarelto | Substudy A: standard of care | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 70 | 73 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 9 (6 to 12) | 8 (5 to 13) | | |

**Statistical analyses**

| **Statistical analysis title** | Analysis primary endpoint substudy A |
|---|---|
| Comparison groups | Substudy A: Xarelto v Substudy A: standard of care |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | > 0.05 |
| Method | Logrank |

Notes:

[1] - Analysis is only exploratory due to premature termination of the study.

**Primary: Primary endpoint substudy C Asunercept**

| | |
|---|---|
| End point title | Primary endpoint substudy C Asunercept |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| Day 1 to day 29 | |

| **End point values** | Substudy C-Asunercept high dose | Substudy C-Asunercept intermediate dose | Substudy C-Asunercept low dose | Substudy C Asunercept standard of care |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 25 | 23 | 26 | 25 |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 10 (7 to 21) | 12 (7 to 13) | 8 (6 to 11) | 7 (5 to 12) |

**Statistical analyses**

| **Statistical analysis title** | Analysis primary endpoint substudy C Asunercept |
|---|---|
| Comparison groups | Substudy C Asunercept standard of care v Substudy C- Asunercept high dose v Substudy C- Asunercept intermediate dose v Substudy C- Asunercept low dose |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | > 0.05 |
| Method | Logrank |

Notes:

[2] - Analysis is only exploratory due to premature termination of the study.

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events: Day 1 to day 29 | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

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

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: All adverse events have been uploaded in PDF

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 28 April 2020 | • Deletion of IMP Chloroquin in main study due to urgent safety measure<br>• Dose increase of IMP Lopinavir/Ritonavir in main study due to new information of required dose in Sars-CoV-2 infection<br>• Additional IMPs for Sub-C: Tocilizumab, Asunercept<br>• Sub-B: Adaptation of blood pressure level<br>• Additional centers: Graz, Neunkirchen, Linz |
| 03 November 2020 | • Inactivation of IMP in main study: Hydroxychloroquine<br>• Additional IMP in main study: Remdesivir (if not part of SOC)<br>• Exchange of IMP in main study: Pooled plasma/IVIg against convalescent plasma<br>• Additional IMP for Sub-C: Pentaglobin<br>• Removal of IMPs for Sub-C: Tocilizumab, Clazakizumab |
| 23 November 2020 | • Remote SDV |
| 15 December 2020 | • Removal of IMP in main study: convalescent plasma |
| 12 February 2021 | • Day 90 Follow-up<br>• Addition of interview study |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported