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Clinical Study Report Summary **Efficacy and safety of Tiprelestat for treatment of severe COVID-19 (COMCOVID trial)** - Prospective, multicenter, randomized, placebo-controlled, double-blind clinical trial in parallel groups -	
Investigational Product:	Tiprelestat (solution for intravenous infusion) or placebo
Indication studied:	Severe COVID-19
Dose and Duration:	100 mg Tiprelestat or placebo twice a day for 7 days or until patient was no longer hospitalized due to COVID-19, if earlier (but at least 4 days for the sentinel patient)
Patient Population:	Adult patients with confirmed COVID-19 hospitalized for COVID-19 treatment with score 4 or 5 according to WHO COVID-19 clinical progression scale
Sponsor:	tiakis Biotech AG (formerly trading as Proteo Biotech AG) Sophienblatt 40, 24103 Kiel (Germany)
EudraCT Number:	2022-000714-33
Protocol Code:	PT26/17/01
Clinical Phase:	Ib / II
Trial Initiation Date: Trial Completion Date:	17 MAY 2023 (first patient first visit) 03 MAY 2024 (last patient last visit / last contact)
Co-ordinating Investigator:	Prof. Dr. med. Michael Dreher Specialist in Internal Medicine / Pneumology Head of Department of Pneumology and Intensive Care Medicine at University Hospital Aachen, Pauwelsstraße 30, 52074 Aachen (Germany)
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Date of the Clinical Trial Report:	18 SEP 2024

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2 CLINICAL STUDY REPORT SUMMARY

Name of Sponsor: tiakis Biotech AG, Kiel, Germany	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient: Tiprelestat (human recomb. Elafin)		

Title of clinical trial:

Efficacy and safety of Tiprelestat for treatment of severe COVID-19 (COMCOVID trial)

Investigators:

Hospital infectiologists, internists and pneumologists experienced in hospitalized COVID-19 patients participated in the trial, for details see list of centers below.

Clinical Trial Centers:

Seven (7) out of 10 initiated centers in Germany (including the center of the coordinating investigator) enrolled at least one patient.

Publication (Reference):

None at date of report

Studied Period (Years): Date of First Enrolment: Date of Last Completed:	approx. 1 year 17 MAY 2023 03 MAY 2024	**Phase of Development:** Ib / II

Objectives:

PRIMARY OBJECTIVES:

- To assess the efficacy of a 7-days treatment with Tiprelestat in patients who have been hospitalized for the treatment of COVID-19
- To assess the safety of Tiprelestat compared to placebo applied in patients who have been hospitalized for the treatment of COVID-19

Clarification Notes:

All of the following details reflect the Clinical Trial Protocol, Version 6.0, 14 JUL 2023, including the changes from Version 5.0 (21 APR 2023) which became necessary to adjust the representativity of the study population to the current situation in hospitals treating patient hospitalized due to COVID-19.

“Severe” in the title reflects the original definition (hospitalized due to Covid-19, among 4 gradings of severity) by the Robert-Koch-Institute in Germany. The efficacy assessments in the study used the finer tuned 11-graded WHO progression scale defining “severe” as hospitalized plus high flow oxygen, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation (score 6 to 9).

Methodology:

Clinical Trial Population

Adult patients with confirmed COVID-19 hospitalized for COVID-19 treatment with score 4 or 5 according to WHO COVID-19 clinical progression scale.

Trial Periods /Visits and Treatment

Center specific usual treatment of COVID-19 was given to the hospitalized patients, and in addition the Investigational Medicinal Product (IMP) for up to 7 days. The clinical trial comprised a treatment period for up to 7 days or until the patient was no longer hospitalized due to COVID-19, if earlier (but at least 4 days for the sentinel patient), i.e. Day 1 to longest Day 8, and a subsequent follow-up period till Day 29 with mortality extension till Day 91.

Efficacy Assessments

- Rating of patient’s clinical status (i.e. 10-points COVID-19 WHO clinical progression-score)
- Oxygen therapy
- Hospitalization due to COVID-19
- Intensive Care Unit (ICU) stay

- Acute kidney injury (AKI),
- Hemofiltration or dialysis techniques
- Active diuresis
- Extracorporeal membrane oxygenation (ECMO)
- Catecholamine administration
- Myocardial arrhythmia
- COVID-19 symptoms “resting dyspnea” and “fatigue”, “exertional dyspnea
- Any other deterioration symptoms and complications of COVID-19
- Mortality

Safety / Tolerability Assessments

- Vital signs, Oxygen saturation (SpO_2)
- Safety laboratory tests: *Hematology, Clinical Chemistry*
- Pregnancy test
- Adverse events (AEs)

Pharmacokinetic (PK) information (whether the IMP accumulates)

Number of Patients:

Planned: 296 patients (148 per treatment group)
Enrolled and analyzed (per treatment group): 17 (9 Tiprelestat, 8 Placebo)

Diagnosis:

COVID-19

Main Criteria for Inclusion:

Inclusion criteria

1. Signed informed consent and data protection declaration prior to initiation of any trial procedures
2. Patient ≥18 years of age at time of enrolment and capable of providing informed consent by him- / herself
3. Patient with COVID-19 fulfilling the following criteria:
    a. first laboratory-confirmation of the current episode of SARS-CoV-2 infection (COVID-19) as determined by PCR or antigen test (no self-tests) in any defined specimen collected within 10 days prior to trial enrolment
    b. hospitalization for COVID-19 treatment
    c. without or with oxygen therapy by mask / nasal prong (score 4 or 5 according to WHO COVID-19 clinical progression scale)

Exclusion criteria

1. Life time expectancy of 2 days or less as judged by the investigator
2. Malignant disease requiring chemotherapy, radiation therapy and / or immune therapy at the time of enrolment
3. Patient requiring dialysis
4. [not applicable anymore]
5. *Only for female patients of childbearing potential:* Pregnancy, positive pregnancy test on Day 1, breast feeding or no effective contraception
6. Current or previous participation within the past 30 days in another interventional clinical trial with an investigational medicinal product
7. Known to be or suspected of being unable to comply with the clinical trial protocol (e.g. no permanent address, history of drug abuse, known to be non-compliant or presenting an unstable psychiatric history)
8. Legal incapacity and / or other circumstances rendering the patient unable to understand the nature, scope and possible impact of the clinical trial
9. Patient in custody by juridical or official order evidence of an uncooperative attitude
10. Patient, who is a member of the staff of the trial center, staff of the sponsor or CRO, the investigator him- / herself or close relatives of the investigator

Investigational Medicinal Products (IMPs)

Test Product (IMP-1):	Tiprelestat (50 mg in 5 mL 0.9% sodium chloride solution per vial)
Control Product (IMP-2)	Placebo (5 mL 0.9% sodium chloride solution)

Mode of Administration:	30-minute infusion via an infusion pump
Dose Regimen:	100 mg Tiprelestat (or placebo) diluted in 100 mL sodium chloride solution twice daily for 7 days or until patient was no longer hospitalized due to COVID-19.
Batch Numbers:	Vial bulk before double-blind labelling: CQ0123 (IMP-1); CP0122 (IMP-2); After double-blind labelling: CQ0123A (for the Sentinel patient), CQ0123B (for 68 patients), CQ0123C (for further 68 patients)

Criteria for Evaluation:

PRIMARY EFFICACY ENDPOINT

- Rating according to the WHO COVID-19 clinical progression scale (WHO-CPS) on Day 9

SECONDARY EFFICACY ENDPOINTS

- Rating according to the WHO COVID-19 clinical progression scale on Day 8
- Rating according to the WHO COVID-19 clinical progression scale on Day 10
- Rating according to the WHO COVID-19 clinical progression scale on Day 14
- Proportion [n/N] of patients discharged from hospital on Day 9
- Number of days with any oxygen support (i.e. WHO COVID-19 clinical progression scale ≥5) *
- Proportion of patients [n/N] with progression to severe disease according to the WHO COVID-19 clinical progression scale (score ≥6) *
- Time to first occurrence of severe disease (score ≥6) according to the WHO COVID-19 clinical progression scale *
- Number of days of severe disease (score ≥6) according to the WHO COVID-19 clinical progression scale *
- Number of days in ICU *
- Number of days with “resting dyspnea” **
- Number of days with “fatigue” **
- Number of days with “exertional dyspnea” **
- 28-day mortality [n/N]
- 90-day mortality [n/N]

* Time frame: Day 1 after randomization to Day 29 or Day 1 after randomization to Day of Discharge, if earlier

** Time frame: Day 1 after randomization to Day 29. If discharged earlier, by phone on Day 29

OTHER / EXPLORATORY EFFICACY ENDPOINTS
(evaluated descriptively only)

- Proportion [n/N] of patients per Day and number of days with assisted mechanical ventilation or ECMO *
- Proportion [n/N] of patients per Day and number of days with acute kidney injury (AKI), requirement of hemofiltration or dialysis techniques or active diuresis (i.e. intravenous diuresis), herein summarized as “relevant renal issues” *
- Proportion [n/N] of patients per Day and number of days with catecholamine administration *
- Proportion [n/N] of patients per Day and number of days with new onset myocardial arrhythmia *
- Proportion [n/N] of patients per Day and number of days with any other deterioration symptoms and complications of COVID-19 *
- Proportion [n/N] of patients per Day and number of days with hospitalization due to COVID-19 *
- Further health status (course of oxygen given, proportion of patients with oxygen therapy) *

* Time frame: Day 1 after randomization to Day 29 or Day 1 after randomization to Day of Discharge, if earlier

SAFETY ENDPOINTS

- Proportion [n/N] of adverse events (AEs) and adverse drug reactions (ARs) *
- Safety laboratory data *

* Time frame: Day 1 after randomization to Day 29 or Day 1 after randomization to Day of Discharge, if earlier

Statistical Methods:

Analysis sets

All 17 subjects who were exposed to IMP were included in the analysis of safety. Efficacy analyses were done in the per protocol set (PPS, N=14), a modified PPS (mPPS, N=13) and the full analysis set (FAS, N=16).

Primary efficacy endpoint

The primary endpoint was analyzed for treatment differences by applying the Generalized Linear Model for categorical data with the multinomial distribution as link function and including the score on Day 9 as dependent variable, with baseline WHO-CPS-score, treatment and chronic kidney/ renal comorbidities (present vs absent) as fixed effects and age as covariate into the model.

Secondary endpoints: efficacy

The secondary efficacy endpoints reflecting *differences in score values* were analyzed analogously to the primary endpoint.

The endpoints reflecting proportions were analyzed by logistic regression model with baseline WHO-CPS-score, treatment and chronic kidney/ renal comorbidities (present vs. absent) as fixed effects and age as covariate.

The endpoints reflecting count variables were analyzed by applying the ANCOVA model with the same independent variables as in the logistic regression model. Remedies for model non-convergence and backward elimination rules for non-relevant independent variables were considered. See section 9.8.3 for more details.

Secondary endpoints: safety / tolerability

Standard descriptive statistics for

- Adverse events (AEs):
- Vital signs
- Safety laboratory parameters
- Pharmacokinetic (PK)

A Data Safety Monitoring Board (DSMB) performed interim assessments after the first patient (sentinel approach) had been treated open label with Tiprelestat for 7 days, and after 12 patients had been treated with IMP.

Summary – Conclusions:

EFFICACY RESULTS:

The trial was powered to show significant efficacy in the primary endpoint in a planned study population of 296 patients. Due to the changes of the COVID-19 pandemic during the study period, only 17 patients could be recruited and treated (9 Tiprelestat, 8 Placebo) because the hospitalization rate due to COVID-19 declined substantially.

In general, the power of the actual small sample size of this study does not allow for any reliable efficacy assessment, neither for the primary, nor the secondary or exploratory efficacy endpoints. The differences between groups regarding efficacy on the COVID-19 endpoints were not consistent with variations of the analysis sets. The results in the different populations show that even a single patient can have a considerable influence on the results. There could be a possible trend, that better adherence to the protocol as reflected by the different analysis sets led to somewhat more favorable results for Tiprelestat. In addition, some imbalances in baseline characteristics suggest, that patients in the Tiprelestat Group were at slightly higher risk for a more severe course of COVID-19 compared to placebo.

Due to the low number of patients, major violations of protocol with impact on primary endpoint had relevant influence on efficacy results depending on the analysis set. Thus, it was post-hoc decided to describe all efficacy results primarily for the mPPS population (N=13) unless otherwise specified.

Primary efficacy endpoint: score in COVID-19 WHO-CPS on Day 9

- From Day 1 (Baseline) to Day 9, mean and median score values decreased comparably in both treatment groups in the PPS and the mPPS, whereas mean and median score values slightly less in the Tiprelestat Group compared to the Placebo in the FAS. The corresponding p-values were >0.5, i.e. statistically significant results in favor of Tiprelestat were not observed.

Secondary efficacy endpoints

- Score values in COVID-19 WHO-CPS decreased in both treatment groups from Day 1 to Day 14.
- 10/13 patients (76.9%) were discharged from hospital until Day 9; 4/5 patients (80.0%) in the Tiprelestat Group and 6/8 patients (75.0%) in the Placebo Group.
- None of the Tiprelestat treated patients developed a severe disease according to the COVID-19 WHO-CPS (score value ≥6) during the 29-day time frame for this endpoint. However, in the FAS (N=16), 1 patient each in both treatment groups had a progression to a severe disease according to COVID-19 WHO-CPS.
- None of the Tiprelestat treated patients died within the first 28-days of this trial (AE recording started on Day 1 and ended on Day 29 or on Day of Discharge, if earlier). One patient of the Tiprelestat Group (in FAS population) died during the 90-day follow-up period, i.e. 38 days after last IMP dose. The investigator

stated, in agreement with the general physician of this patient, that this death resulted from the general multimorbidity of this 75-year-old patient. Considering this opinion and the long period between the last administration of IMP and the time of death, no causal relation between treatment with Tiprelestat and the death of this patient is assumed.

- The number of days with any oxygen support (i.e. COVID-19 WHO-CPS ≥5 score points) was lower in the Tiprelestat Group (2.4 ± 3.6 days) compared to Placebo (4.0 ± 6.2 days).
- No patient had days with severe disease in the Tiprelestat Group. The mean (± SD) number of days with severe disease (i.e. COVID-19 WHO-CPS ≥6 score points) was comparable in both treatment groups (Tiprelestat: 0 days; Placebo: 1.3 ± 3.5) and ranged from 0 to 10 days in the Placebo Group.
- Days with ICU stay occurred in the Placebo Group (mean ± SD: 1.8 ± 4.6 days, range: 0 – 13 days) and in the Tiprelestat Group only in FAS (1.4 ± 3.9 days, range 0 – 11 days), but not in PPS and mPPS.
- The mean (± SD) number of days with resting dyspnea was marginally lower in the Tiprelestat Group (9.6 ± 10.2 days, range 1 – 25 days) compared to the Placebo Group (10.5 ± 13.5 days, range 0 – 28 days).
- The mean number of days with fatigue was comparable in both treatment groups (Tiprelestat Group: 19.6 ± 10.7 days), Placebo: 20.0 ± 12.4 days).
- The mean (± SD) number of days with exertional dyspnea was higher in the Tiprelestat Group (19.6 ± 12.9 days) compared to the Placebo Group (15.8 ± 13.0 days), while the range between minimum and maximum number of days with exertional dyspnea was comparable between both treatment groups.

Exploratory endpoints

- None of 17 treated patients (100.0%) needed any assisted mechanical ventilation or ECMO during the time frame for this endpoint.
- Relevant renal issues were not reported for any patient in the Tiprelestat Group in the mPPS and the PPS, but for 1/8 patients (12.5%) in the FAS during the time frame for this endpoint after baseline. In 2/8 patients (25.0%) a relevant renal issue was reported in the Placebo Group during the time frame for this endpoint. The mean (± SD) number of days with relevant renal issues after day 1 was lower in the Tiprelestat Group (0 ± 0) than in the Placebo Group (1.5 ± 4.2) and ranged from 0 to 12 days in the Placebo Group during this time period.
- None of the patients in the Placebo Group and in the PPS and mPPS of the Tiprelestat Group had a catecholamine administration during the time frame for this endpoint, but 1 patient treated with Tiprelestat in the FAS.
- New onset of myocardial arrhythmia was not observed in the mPPS of the Tiprelestat Group (2/8 in the FAS and 1/6 in the PPS), and in 1/8 patients (12.5%) in the Placebo Group during the time frame for this endpoint with mean (± SD) number of days of 1.6 ± 4.6 days.
- The proportion of patients with other deterioration symptoms of COVID-19 varied between 1 and 2 patients in both treatment groups. The mean ± SD number of days with other deterioration symptoms of COVID-19 was slightly higher in the Placebo Group (2.1 ± 4.6 days compared to any analysis set in the Tiprelestat Group (mean ± SD) between 0.3 ± 0.5 days to 0.4 ± 0.5 days).
- All 17 treated patients (100.0%) were hospitalized due to COVID-19 on Day 1. From Day 2 to Day 14, the number of patients hospitalized decreased in both treatment groups. The mean ± SD number of days with hospitalization due to COVID-19 was comparable in both treatment groups (mPPS of the Tiprelestat Group: 4.0 ± 3.1 days, Placebo Group: 4.3 ± 3.7 days) and ranged from 1 to 9 days in the mPPS of the Tiprelestat Group and from 1 to 13 days in the Placebo Group.
- In the mPPS, the proportion of patients and the mean number of days with oxygen therapy was lower in the Tiprelestat Group (2/5 patients, 40.0%, 2.4 ± 3.6 days) compared to the Placebo Group (5/8 patients, 62.5%, 4.0 ± 6.2 days) during the time frame for this endpoint.
- On Day 1, the mean (± SD) values of the SpO2 were slightly higher (i.e. better) in the Placebo Group (95.3 ± 2.7%) compared to any analysis set in the Tiprelestat Group (mean ± SD between 90.8 ± 7.3% to 92.1 ± 5.5%). Whereas the mean ± SD values remained almost unchanged in the Placebo Group during the clinical trial, the mean ± SD values improved in all analysis sets of the Tiprelestat Group (mean ± SD) on Day 9: ranging between 95.0% to 95.8 ± 1.1%.

SAFETY RESULTS:

Adverse events

In total 12 TEAEs occurred in 7/17 patients (41.2%): 3/9 patients (33.3%) experienced 5 TEAEs in the Tiprelestat Group and 4/8 patients (50.0%) experienced 7 TEAEs in the Placebo Group. All reported TEAEs were mild to moderate

in intensity. None of the TEAEs was serious and none led to treatment discontinuation or premature trial discontinuation. In the Placebo Group, 1 TEAE was considered as related to the IMP, whereas none of the reported TEAEs in the Tiprelestat Group was considered as related to the IMP. 9 TEAEs in 5/17 patients (29.4%) had resolved and a total of 3 TEAEs experienced by 2/17 patients (11.8%) had not resolved until the end of the up to 29-day AE recording period. Post-treatment AEs were reported for patients in the Tiprelestat Group only: 2 post-treatment AEs were reported in 2/9 patients (22.2%), all of mild to moderate intensity and considered as not related to IMP. None of the post-treatment AEs led to premature trial discontinuation. 1 post-treatment AE occurred in 1/9 patients (11.1%) each had resolved respectively not resolved by the end of the AE recording period.

Clinical laboratory evaluation

In general, no relevant abnormalities in the laboratory blood parameters were suspected to be related to the administration of Tiprelestat.

Vital signs

Overall, no clinically relevant changes were observed in mean values of systolic and diastolic blood pressure, pulse rate and body temperature in both treatment groups during this clinical trial.

Treatment with 100 mg Tiprelestat infusion solution b.i.d. (200 mg /day) for up to 7 days was found to be safe and well tolerated.

Pharmacokinetics

Results of PK information show, that the IMP does not accumulate in blood plasma upon repeated administration for up to 7 days.

CONCLUSION:

In this clinical trial the differences between groups regarding efficacy on the COVID-19 endpoints are not consistent with variations of the analysis sets due to low sample size. Therefore, no conclusion on the efficacy analysis can be drawn for either the primary endpoint or the secondary endpoints and exploratory endpoints. However, and in accordance with previous clinical trials, the results show that Tiprelestat was safe and well tolerated in this trial, i.e. also when administered as infusion in multiple dose regimen over 7 days. In addition, results of Pharmacokinetic information show, that Tiprelestat does not accumulate in blood plasma.

Date of Report: 18 SEP 2024