CLINICAL STUDY REPORT SUMMARY

A Randomized, Placebo Controlled, Double Blind Study to Evaluate the Safety and Efficacy of Rabeximod Compared to Standard of Care in Patients with Moderate Coronavirus Disease (Covid-19)

<table>
<tr><td>Name of Sponsor/Company:
Cyxone AB</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Not applicable</td></tr>
<tr><td>Name of Active Ingredient:
Rabeximod</td></tr>
<tr><td colspan="3">Title of Study: A Randomized, Placebo Controlled, Double Blind Study to Evaluate the Safety and Efficacy of Rabeximod Compared to Standard of Care in Patients with Moderate Coronavirus Disease (Covid-19)</td></tr>
<tr><td colspan="3">Investigators: The entire listing of all Investigators can be found in Appendices 16.1.6.1-16.1.6.6.</td></tr>
<tr><td colspan="3">Study centres: 19 centres in Poland (6), Ukraine (3), Slovakia (3), Latvia (3) and Hungary (4) enrolled subjects in the study.</td></tr>
<tr><td colspan="3">Publications (reference): Not applicable</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient treated: January 17, 2021
Date last patient completed: August 10, 2021</td><td>Phase of development:
2</td></tr>
<tr><td colspan="3">Objective and endpoints:
Objective:
• To evaluate the efficacy and tolerability of rabeximod in the treatment of patients with moderate Covid-19.

Primary endpoint:
• The proportion of patients alive and free of respiratory failure (i.e., need for invasive mechanical ventilation, non-invasive ventilation, high-flow nasal cannula oxygen, or ECMO) at Day 28.

Secondary endpoints:
• Time to response (TTR) (in days).
Response to treatment was defined as the reduction of at least one severity level on the World Health Organization Ordinal Scale for Clinical Improvement (WHO-OSCI). The WHO-OSCI is an ordinal scale of 9 severity levels (from 0 to 8) for Covid-19.
• To evaluate the impact of rabeximod on the clinical, laboratory, respiratory parameters and viral load, the following clinical and respiratory parameters were assessed:
o ICU admission rate. The percentage of patients admitted to the ICU in the rabeximod group as compared with controls (Time frame: Day 60)</td></tr>
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- Discharge rate. The percentage of patients discharged in the rabeximod group as compared with controls. (Time frame: Day 28)
- Duration (cumulative days) of mechanical ventilation (Time frame: Day 60)
- Duration (cumulative days) of extracorporeal membrane oxygenation (Time frame: Day 60)
- Duration (cumulative days) of supplemental oxygenation (Time frame: Day 60)
- Time to SARS-CoV-2 RT-PCR negativity in upper respiratory tract specimens (Time frame: Day 28)
- Change (reduction) in SARS-CoV-2 viral load in upper respiratory tract specimens as assessed by area under viral load curve (Time frame: Day 28 compared to baseline)
- Mortality rate at Day 7, Day 14, Day 28, Day 60
- To assess the safety of rabeximod combined with standard of care therapy in terms of serious or non-serious adverse events incidence rate. All adverse event recording.

Exploratory endpoints:

- Rabeximod concentration in plasma during the 14-day treatment period.

Methodology: This was a multicentre, randomized, double-blind, placebo-controlled study of orally administered rabeximod in a total of 92 patients with moderate coronavirus disease (Covid-19).

Eligible patients who consented to the study were randomly assigned (in a 1:1:1 ratio) to receive Investigational product (IP) (i.e., rabeximod 15 mg, rabeximod 30 mg or placebo) once daily orally for 14 days, in addition to receiving their standard of care treatment. During the treatment period, the health status of patients was closely monitored, and clinical and laboratory data was collected at a high frequency

Patients were discharged on Day 14 (or earlier if the patients displayed an accelerated health status improvement) and were invited back for a study visit on Day 28 followed by a phone visit on Day 60.

In case the patient needed to continue the treatment longer than the initially scheduled 14 days then that patient was permitted to continue receiving the assigned study treatment (in the hospital or at home) until the investigator decided to stop the administration or Day 28, whichever came first.

If a patient was discharged from the hospital earlier due to improvement in the disease, the treatment with IP was allowed to be stopped.

Number of subjects (planned and analysed)

In total, 300 patients were planned to be randomized to receive IP.

117 patients were screened and 92 were randomized, all of whom were included in the efficacy and safety analyses.

Inclusion and exclusion criteria:

Inclusion criteria

1. Willing and able to provide written informed consent prior to performing study procedures.
2. SARS-CoV-2 positivity of the nasal/throat-swab/saliva by reverse-transcriptase-polymerase chain- reaction (RT-PCR) assay tested by the local diagnostic laboratory ≤4 days before randomization.
3. Currently hospitalized or requiring hospitalization for the Covid-19 medical care.
4. Age >18 and <85 years.
5. Presence of at least 3 of the following symptoms as present: fever, cough, myalgia, fatigue.

6. Saturation of oxygen (SpO_2) > 93%, with or without oxygen therapy ≤ 2 days before screening.
7. Agreed to use an acceptable method of contraception for the duration of the study or not be of childbearing potential. Female patients of childbearing potential had to agree to use an acceptable and effective barrier method of contraception (for example, diaphragm with spermicide, or condom with spermicide) prior to study entry (baseline visit) and for the duration of the study and for a period of 30 days after all study procedures are completed. If the patient became pregnant during participation in the study or within 30 days after stopping the study drug treatment, the study doctor or study staff had to be informed immediately. The study drug was stopped and the patient's participation in the study were ended.

   Male patients were informed about the importance of avoiding getting a female partner pregnant during the study. The patient had to agree to use an acceptable and effective barrier method of contraception (for example, condom with spermicide) prior to study entry and for the duration of the study and for a period of 90 days after all study procedures are completed.

   If the patient's female partner became pregnant during participating in this study or within 90 days after stopping the study drug treatment, the study doctor or study staff had to be informed immediately.

Exclusion criteria

1. Pregnant, or intend to become pregnant or breastfeed during the study.
2. Patients who are unable to swallow the capsule.
3. Require invasive mechanical ventilation, including extracorporeal membrane oxygenation at study entry
4. Receiving cytotoxic or biologic treatments (such as tumour necrosis factor inhibitors, anti-interleukin-1, anti-IL-6 (tocilizumab or sarilumab), T-cell or B-cell targeted therapies (rituximab), interferon, or Janus kinase inhibitors for any indication at study entry. A washout period 4 weeks (or 5 half-lives, whichever is longer) is required prior to screening.
5. Ever received convalescent plasma or intravenous immunoglobulin for Covid-19.
6. Have received high dose corticosteroids at doses >20 mg per day (or prednisone equivalent) administered for ≥14 consecutive days in the month prior to study entry.
7. Have diagnosis of primary tuberculosis (TB) or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines (by history only, no screening tests required).
8. Suspected serious, active bacterial, fungal, viral, or other infection (besides Covid-19) that in the opinion of the investigator could constitute a risk when taking investigational product.
9. Have received any live vaccine within 4 weeks before screening, or intend to receive a live vaccine during the study. Use of non-live (inactivated) vaccinations is allowed.
10. Current diagnosis of active malignancy that, in the opinion of the investigator, could constitute a risk when taking investigational product.
11. Have a history of venous thromboembolism (VTE) (deep vein thrombosis (DVT) or pulmonary embolism (PE)) within 12 weeks prior to randomization or have a history of recurrent (>1) VTE (DVT/PE).
12. Anticipated discharge from the hospital, or transfer to another hospital (or another unit), which is not a study site within 72 hours after study entry.
13. Have neutropenia (absolute neutrophil count <1000 cells/μL).
14. Have lymphopenia (absolute lymphocyte count <200 cells/μL).
15. Have alanine aminotransferase or aspartate aminotransferase >5x upper limit of normal.

16. Have total bilirubin > 1.5 x upper limit of normal.
17. Estimated glomerular filtration rate <30 millilitres/minute/1.73 m^2.
18. Have a known hypersensitivity to rabeximod or any of its excipients.
19. Are currently enrolled in any other clinical study involving an investigation product or any other type of medical research judged not to be scientifically or medically compatible with this study. The participant should not be enrolled (start) in another clinical study for the treatment of Covid-19 or SARS CoV-2 through Day 28.
20. Are using or will use extracorporeal blood purification device to remove proinflammatory cytokines from the blood such as a cytokine absorption or filtering device, for example, CytoSorb®.
21. Are unlikely to survive for at least 48 hours after screening in the opinion of the investigator.

Test product, dose and mode of administration, batch number: Either 30 mg or 15 mg of rabeximod 15 mg gelatine capsules were administered orally once a day for 14 days, batch number #201293767.

Reference therapy, dose and mode of administration, batch number: Placebo gelatine capsules similar to test product in appearance and content, excluding the active ingredient, were administered orally once a day for 14 days, batch number #201293764.

Criteria for evaluation:

Efficacy: Hospital discharges and mortality were counted. All patients were monitored daily for vital signs and clinical parameters including respiratory-pulmonary measures to determine the WHO-OSCI scores. Nasopharyngeal swabs were collected for determining the presence of the SARS-Cov-2 virus and the viral load.

Safety: Adverse events (AEs) and serious AEs (SAEs) were recorded throughout the study. Vital signs, clinical parameters, blood chemistry and haematology were monitored at high frequency until discharge and then later at the follow-up visits. ECGs were recorded at screening and after the hospital discharge.

Exploratory: Rabeximod pharmacokinetics samples.

Statistical methods:

Sample size calculation

An observational, retrospective, longitudinal multicentre-study in hospitalized patients with Covid-19 moderate pneumonia to evaluate the 2-week effectiveness and safety of baricitinib combined with antivirals (lopinavir/ritonavir) compared with the standard of care therapy which was hydroxychloroquine and lopinavir/ritonavir[1], was used to estimate the initial sample size for this clinical study as one of the few relevant published studies which was available at the planning stages of the RBMCovi19 study. From their efficacy data it was projected that this study would have to recruit at least 100 patient per study arm, i.e., 300 patients in total.

During the study recruitment period, however, new clinical data continued to emerge from studies with drug candidates targeting similar pathways to address Covid-19. Thus, results from other Phase 2 studies were used to establish that for rabeximod to stay competitive with other drugs targeting similar pathways, it had to show efficacy signal at the level of 30 patients per study arm. Hence, the recruitment into the study was stopped when 92 patients had been randomized.

Analysis populations

- Intent-to-Treat (ITT) population: as all patients who were randomized. Patients were analysed in the treatment group they were randomized to, regardless of the actual treatment received. The ITT population was the primary analysis population for efficacy.

1 Cantini, F., L. Niccoli, C. Nannini, D. Matarrese, M. E. D. Natale, P. Lotti, D. Aquilini, G. Landini, B. Cimolato, M. A. D. Pietro, M. Trezzi, P. Stobbione, G. Frausini, A. Navarra, E. Nicastri, G. Sotgiu, and D. Goletti. 2020. 'Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study', J Infect, 81: 647-79.

- Per Protocol (PP) population: as all patients who completed the protocol without a major protocol deviation. Efficacy analysis was repeated on the PP population as secondary analysis.
- Safety population: as all patients who received at least one dose of IP. Patients were analysed according to the actual treatment they received. The safety population was used for all safety analyses.

Analysis of efficacy data

Primary endpoint

The primary null hypothesis tested in the study was if the proportion of patients alive and free of respiratory failure 28 days after the start of the treatment was equal in patients randomized to 15 mg and 30 mg of rabeximod, respectively, compared to patients randomized to receive placebo. The alternative hypothesis was that the response rate was different between the groups. The primary comparison was 30 mg versus placebo and as a secondary (to control the family-wise type 1 error rate) comparison the hypothesis that 15 mg and placebo were equal was tested.

Secondary endpoints

Secondary endpoints were categorized into the following groups:

a) Time to (from start of treatment)
   - response, or
   - SARS-CoV-2 RT-PCR negativity

   were displayed with Kaplan-Meier survival curves and tested with log-rank test. Dead patients were counted as non-responders in both analyses.

b) Incidence of patients
   - admitted to ICU by Day 60, or
   - discharged from hospital by Day 28

   were compared between treatment groups with Fisher's exact test. Alive status had no impact on these measures as they were not time-dependent, it could be clearly identified for a patient if he/she was admitted to ICU or discharged from hospital.

c) Duration (days) of
   - mechanical ventilation, or
   - extracorporeal membrane oxygenation, or
   - supplemental oxygenation

   from Day 1 to Day 60 were treated as continuous variables and treatment groups were compared with Kruskal-Wallis test followed by the Wilcoxon rank sum test (comparisons between each pair of treatment groups). Differences between treatment groups were provided with 95% confidence intervals based on the Hodger-Lehmann estimator.

d) SARS-CoV-2 viral load in upper respiratory tract specimens, as estimated by area under viral load curve (calculated by the trapezoid formula), was handled as a continuous variable. Treatment groups were compared with Kruskal-Wallis test followed by Wilcoxon rank sum test when comparing the groups in pairs, differences between treatment groups were provided with 95% confidence intervals based on the Hodger-Lehmann estimator.

e) Overall survival from Day 1 to Day 60 was presented using Kaplan-Meier curves and treatment groups compared in pairs with log-rank test. Proportion of patients dead by Day 7, Day 14, Day 28 and Day 60 were reported by treatment groups, with 95% confidence intervals and the associated p-value calculated by the Fisher's exact test.

Exploratory endpoints

a) Rabeximod concentration in plasma was presented by collection time during the 14 days of treatment period. The observations were described by group by descriptive statistic, i.e., the number of observations minimum value, median, maximum value, mean and standard deviation.

Analysis of safety data

AEs were classified using MedDRA coding. For the analysis of AEs, summary tables with descriptive statistics were generated for the incidence of any AEs, SAEs, severe AEs, related AEs, and related SAEs by treatment.

Summary of results:

92 patients were randomized (30 patients each to the rabeximod 30 mg and 15 mg groups and 32 to the placebo group) and 81 patients (88.0%) completed the study. 11 patients (4 [13.3%] patients in the rabeximod 15 mg group and 7 [21.9%] patients in the placebo group) discontinued the study.

Efficacy results

Primary endpoint

- In the ITT population (n=92), 30 (100.0%) of the rabeximod 30 mg patients, 29 (96.7%) of the rabeximod 15 mg patients and 31 (96.7%) of the placebo patients were cured, i.e., alive and free of respiratory failure at Day 28. Neither cure rate nor survival rates achieved statistically significant differences between the treatment groups. Based on this finding, the primary null hypothesis of the study could not be rejected.

Secondary endpoints

- TTR:

  The mean TTR was 12.1±8.9 days in the rabeximod 30 mg group (Hazard ratio 1.41 vs placebo), 8.9±7.6 days in the rabeximod 15 mg group (Hazard ratio 1.08 vs placebo) and 10.5±6.5 days in the placebo group. The differences between the rabeximod groups and placebo did not achieve statistical significance.

- ICU admissions:

  No patients in the rabeximod 30 mg group were admitted to ICU, while 1 patient each was admitted to ICU in the rabeximod 15 mg (3.33%) and placebo groups (3.13%).

- Discharge incidences:

  56 patients (18 of 28 [64.3%] in the rabeximod 15 mg group, 12 of 30 [40.0%] in the rabeximod 30 mg group and 14 of 27 [51.9%] in the placebo group) were discharged from hospital due to improvement of the health status between Day 2 and Day 14. The differences between the rabeximod groups and placebo did not achieve statistical significance.

- Mechanical ventilation:

  1 patient randomized to rabeximod 15 mg dose required mechanical ventilation for 1 day.

- Extracorporeal membrane oxygenation:

  No patients had a need for extracorporeal membrane oxygenation during the study.

- Duration of supplemental oxygen:

  21 patients in the rabeximod 30 mg group, 18 patients in the rabeximod 15 mg group and 17 patients in the placebo group received supplemental oxygenation. The mean durations were 7.4±7.3 days in the rabeximod 30 mg group, 5.4±4.7 days in the rabeximod 15 mg group and 6.9±4.3 days in the placebo group. The differences between the rabeximod groups and placebo did not achieve statistical significance.

- Time to SARS-CoV-2 RT-PCR negativity (viral clearance):

Viral clearance expressed as Covid-19 RT-PCR negativity in upper respiratory tract specimens up to Day 28 was achieved in 28 patients (100.0% of the analysed patients) of the rabeximod 30 mg group, 24 (92.3% of the analysed patients) of the rabeximod 15 mg recipients and 26 (96.3% of the analysed patients) of the placebo recipients by Day 28. The Kaplan-Meier estimate in all groups was 7 days. The differences of time to viral clearance between the rabeximod groups and placebo did not achieve statistical significance.

- Change in viral load:

  Change (reduction) in viral load up to Day 28 was achieved in 13.0±13.2 days in the rabeximod 30 mg group, 25.3±36.9 days in the rabeximod 15 mg group and 23.6±32.9 days in the placebo group. There were no statistically significant differences between the treatment groups in change in the SARS-CoV-2 viral load during the trial.

- Mortality rate:

  1 patient died in the rabeximod 15 mg group (at Day 16), and 1 patient died in the placebo group (at Day 7). There were no statistically significant differences between the treatment groups in mortality rate during the trial.

Exploratory endpoints

Average plasma concentrations of rabeximod correlated well with the administered doses.

Safety results

Rabeximod was found generally to be safe and well tolerated. Overall, 51 patients (55.4%) experienced in total 136 TEAEs during the trial. There were no clear differences between the 3 treatment groups for the overall incidences of AEs.

The most frequently reported AEs (by system organ class) of patients overall were associated with metabolism and nutrition disorders (51.09% of patients), infection and infestations (43.48% of patients), investigations (38.04% of patients), and vascular disorders (30.43% of patients). The most frequently reported AEs (by preferred term) of patients overall were hypertension, COVID-19, obesity, type 2 diabetes mellitus, COVID-19 pneumonia, and hypertransaminasemia.

Most AEs were mild or moderate in nature. While there was a somewhat higher number of mild AEs in both rabeximod dose groups than in the placebo group, there was no noticeable difference between the study groups at other levels of severity. Most AEs were unrelated to study drug and the number of possibly or probably related AEs was higher in the rabeximod 15 mg group than in the rabeximod 30 mg or placebo groups.

4 patients experienced in total 4 SAEs leading to discontinuations from the trial including death in 2 patients. 2 other patients, both in the placebo group, discontinued the trial due to AEs. All SAEs leading to discontinuations were judged as unrelated to trial drug.

There were fewer clinically significant abnormal laboratory results in the rabeximod 30 mg group than in other treatment groups: 27 in the rabeximod 30 mg group, 58 in the rabeximod 15 mg group and 127 in the placebo group.

No statistically significant differences in vital signs between the study groups were observed.

The highest number of abnormal physical examination results were observed in the lungs most probably due to underlying COVID-19 infection, but there were no statistically significant differences between the study groups.

2 clinically significant abnormal ECG results (1 in the rabeximod 15 mg group and 1 in the placebo group) were observed during the first study week (i.e., at Day 7) and cleared afterwards and no more clinically significant abnormal ECG results were reported.

Conclusions:

In this randomized, double-blind, placebo-controlled, multi-centre Phase 2 study to evaluate the efficacy and tolerability of rabeximod 15 mg and 30 mg in the treatment of patients with moderate Covid-19 it was shown that:

- Rabeximod was safe and well-tolerated and there were no clear differences between the rabeximod groups and placebo for any of the assessed safety variables.
- The study did not meet its primary endpoint, i.e., rabeximod at 30 mg or 15 mg did not improve the cure rate, i.e., the proportion of patients alive and free of respiratory failure (i.e., a need for invasive mechanical ventilation, non-invasive ventilation, high-flow nasal cannula oxygen, or ECMO) at Day 28 were not statistically significant different between the rabeximod groups and placebo.
- None of the secondary endpoints showed any statistically significant differences between the rabeximod groups and placebo.
- The plasma concentrations of rabeximod correlated well with the administered doses.

Date of the report: 27th May, 2022