Clinical Trial Protocol

Protocol Number:	VP-C21-008
Title:	A randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care in adult subjects with COVID-19**.**
Brief Title:	A trial to investigate recovery from COVID-19 with C21 in adult subjects
Acronym:	ATTRACT-3
Trial Phase:	3
Compound:	C21 (Compound 21)
Version:	5.0
Sponsor:	Vicore Pharma AB Kronhusgatan 11 SE-411 05 Gothenburg, Sweden
EudraCT No.	2021-000264-29

Medical Monitor Coverage Contact Information

The Principal Investigators (PIs) are responsible for ensuring that procedures and expertise are available to handle any potential medical emergencies occurring during the trial. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 8.5.

The Sponsor CRO provides a 24-hour, 7-days a week (24/7) phone service for all active sites, their PIs and site support staff for urgent cases. 24/7 medical monitoring service is available for any medical or safety issues related to subjects included in the trial or subjects screening for participation in the trial.

Medical Monitoring support center contact information:

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care in adult subjects with COVID-19.

Brief Title: A trial to investigate recovery from COVID-19 with C21 in adult subjects.

Rationale: The corona virus disease 2019 (COVID-19) is an ongoing pandemic caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Although several therapeutic agents have been evaluated for the treatment of COVID-19, the morbidity and mortality are still significant. The need for safe, effective, and convenient COVID-19 drugs is likely to remain even after the launch of vaccine programs. The safety and efficacy of C21 in subjects with COVID-19 have been investigated in a phase 2 trial. The results show that C21, as add on to standard of care (SoC), reduced the need for extended oxygen supplementation and had a favorable benefit/risk profile. The rationale for conducting this phase 3 trial is to confirm the efficacy of C21 in subjects with COVID-19.

Objectives, Endpoints and Estimands:

Objectives	Endpoints
Primary	
• Evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19.	• All-cause mortality up to Day 60.
Key secondary	
	• Time to sustained hospital discharge up to Day 60. • Supplemental oxygen free days up to Day 29. • Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5, at Day 15. • Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15.
Secondary	

• Evaluate the safety profile of C21 versus placebo as add on to SoC in subjects with COVID-19.	• Adverse events (AE)s. • Serious AEs (SAE)s. • Changes in safety laboratory assessments. • Withdrawals due to AEs.
• Characterize the PK profile of C21 in subjects with COVID-19.	• PK parameters.
• Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19.	• Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29. • Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, extra corporeal membrane oxygenation (ECMO) or supplemental oxygen use at Days 8, 15, 22, 29 and 60. • Proportion of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60. • Duration of hospitalization, including re-hospitalization, up to Day 60. • Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60. • Duration of intensive care unit stay, including re-admission, up to Day 60. • Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60. • Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60, and respiratory failure free days up to Day 60. • All-cause mortality up to Days 8, 15, 22 and 29. • Change from baseline in peripheral capillary oxygen saturation (SpO_2) /

	fraction of inspired oxygen (FiO_2) at Day 15.
Exploratory	
• To explore the effect of C21 versus placebo as add on to SoC on inflammation.	• Change from baseline in CRP at Day 15.
• To explore the effect of C21 versus placebo as add on to SoC on lung injury.	• Change from baseline in lactate dehydrogenase (LDH) at Day 15.

Primary Estimand:

All-cause mortality up to Day 60 defined as the time to day of death from any cause assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects with no confirmed death before or at Day 60 being censored at day of withdrawal/Day 60 follow-up. The stratified log-rank test will be used to compare the treatments. The treatment difference will be expressed as a hazard ratio with 95% confidence intervals.

Overall Design:

This trial is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter trial to evaluate the efficacy and safety of C21 versus placebo as add on to SoC in adult subjects with COVID-19.

The trial will enroll a total of maximum 300 subjects, 150 per arm (oral C21 100 mg twice a day (b.i.d.) or placebo for 14 days) according to the 1:1 randomization.

Randomization will be stratified by:

- Disease severity (8-point ordinal scale score at Day 1, score 5 or 6).
- Region (North America, South and Central America, Europe, Africa, or Asia).

Approximately 350 subjects will be screened to achieve maximum 300 enrolled and randomly assigned subjects to investigational medicinal product (IMP) treatment.

An independent data monitoring committee (DMC) will review unblinded safety data from the trial after data collection for at least 15 days on the first 150 randomized subjects. In addition, the DMC members may call for an *ad hoc* safety review meeting at any time during the trial.

The trial consists of 3 consecutive periods: a screening period of up to 48 hours, a 2-week IMP treatment period and a follow-up period of up to 7 weeks after last IMP intake. Daily visits are required until discharge. Discharged subjects will return to the clinic for the Day 15 visit. Days 8, 22, 29 and 60 visits will be conducted as phone or video visits for discharged subjects.

All subjects will undergo a series of efficacy, safety, and laboratory assessments. Safety laboratory tests and samples for future exploratory analysis will be obtained at the screening

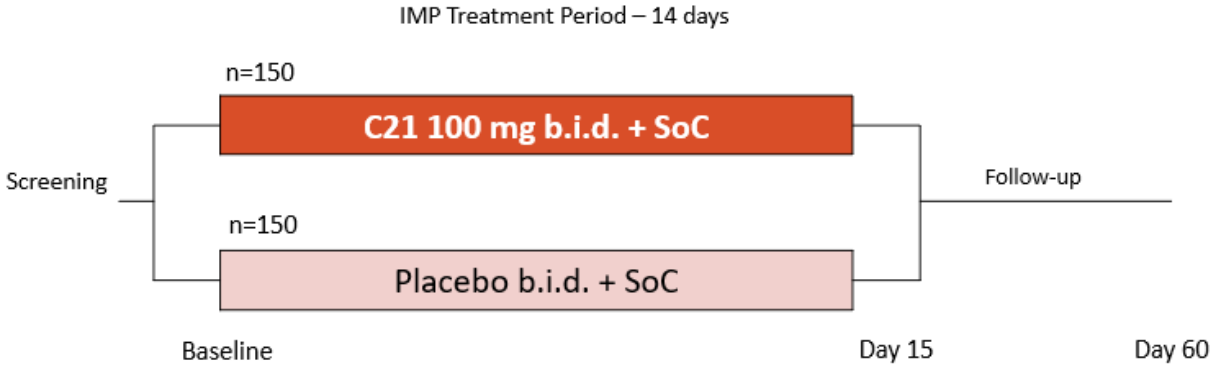
visit, Day 1 (prior to treatment) and Days 3, 5, 8, 11 and 15. Laboratory samples will not be collected at Days 3, 5, 8 and 11 if the subject is discharged from the hospital prior to the visit.

The trial duration for an individual subject will not exceed 9 weeks. End of trial is defined as last subject's last follow-up visit.

The primary endpoint in the trial is all-cause mortality up to Day 60.

The key secondary endpoints are time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15. Type 1 errors will be controlled using a fixed sequential testing hierarchy.

1.2. Schema



1.3. Schedule of Activities (SoA)

	Screening	IMP Treatment Period				In-patient Stay[1)]	Follow-up Period[2)]			Unsche-duled[3)]
Visit	**V1**	**V2**	**V3-15**[1) 4)]	**V16**[4)]	**EWD**[5)]	**V17-29**	**V30**	**V31**	**V32**	**UV**
Day (Visit window)	Up to 48h prior to V2	**Day 1**	**Days 2-14**	**Day 15** (+1 day)		**Days 16-28**	**Day 22** (±1 days)	**Day 29** (±1 days)	**Day 60** (±3 days)	
Eligibility/General										
Informed consent	X									
Eligibility criteria	X	x[6)]								
Demographics	X									
Medical history	X									
IMP and Concomitant Therapy										
Randomization		x								
IMP administration[7)]		x	x							(x)
Check of fasting criteria		x	x							(x)
IMP accountability			x[8)]	x	x					
Previous and concomitant therapy	X	x	x	x	x	x	x	x		(x)
Trial Assessments and Procedures										
8-point ordinal scale	X	x	x	x	x	x	x	x	x	(x)
Supplemental O_2	X	x	x	x	x	x	x	x		(x)
Oxygen saturation	X	x	x	x	x	x				(x)
Hospitalization	X	x	x	x	x	x	x	x	x	(x)
Physical examination	X			x	x					(x)
Body weight and height	X									
Vital signs	X	x	x	x	x	x				(x)
12-lead ECG[9)]	X									(x)
Adverse events	X	x	x	x	x	x	x	x	x[10)]	x
Biochemistry[11)]	X	x[12)]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Haematology[11)]	X	x[12)]	Days 3, 5, 8, 11 (all ± 1 day)	x	x					(x)
Urinanalysis[11)]	X	x[12)]		x	x					(x)
Pregnancy testing[13)]	X			x	x					(x)
Oropharyngeal swab		x								
Pharmacokinetics[14)]		x								
Blood sample for future exploratory analysis		x[12)]		x	x					

1. Daily visits until discharge. Visits will be re-initiated in case of a COVID-19 related hospital re-admission.
2. Follow-up visits by phone or video.
3. Assessments marked with () will be performed per investigator judgment at e.g., COVID-19 related hospital re-admission after Day 29.
4. Days 8 and 15 visits must be performed for all subjects. If a subject is discharged before Day 8, the Day 8 visit will be done by phone or video. Site assessments e.g., oxygen saturation, vital signs and blood sampling will not be performed.
5. An early withdrawal (EWD) visit should be performed for subjects withdrawn from the trial prior to Day 15 (Visit 16).
6. Re-evaluation of eligibility including evaluation of electrocardiogram (ECG) and laboratory results from screening.
7. IMP is administered b.i.d. from Days 1 to 14.
8. IMP accountability will be performed at hospital discharge.
9. A historical 12-lead ECG is acceptable. The ECG should be ≤2 days old at the time of screening (Visit 1).
10. SAEs only.
11. Blood samples taken at screening will be analyzed locally. Samples taken at Days 1 to 15, or at the EWD visit will be analyzed at a central laboratory (if needed due to special circumstances e.g. delays in turn-around time due to COVID-19, blood samples may be analyzed locally after sponsor approval). Days 3, 5, 8 and 11 samples will only be collected if the subject is hospitalized.
12. Blood sampling and urinalysis must be performed prior to IMP dosing.
13. Applicable in women of childbearing potential. If positive, the urine dipstick will be followed up by a blood test.
14. Pharmacokinetic (PK) samples will be collected in a subgroup of approximately 10 subjects.

2. Introduction

C21 is a first-in-class, low molecular weight, orally available, potent, and selective angiotensin II type 2 receptor (AT2R) agonist being developed for treatment of COVID-19 and fibrotic lung diseases such as idiopathic pulmonary fibrosis.

2.1. Trial Rationale

Although several therapeutic agents have been evaluated for the treatment of COVID-19, the morbidity and mortality are still significant, and the need for safe, effective, and convenient COVID-19 drugs is likely to remain even after the launch of vaccine programs.

The recently completed phase 2 trial in hospitalized patients with COVID-19 (VP-C21-006) showed that C21 on top of standard of care significantly reduced the need for extended oxygen supplementation and had a favorable benefit/risk profile. The rationale for conducting this phase 3 trial is to confirm the efficacy and safety of C21 in a larger group of COVID-19 patients.

2.2. Background

COVID-19

In January 2020, SARS-CoV-2 was identified as the causative agent of an outbreak of the new viral pneumonia disease, COVID-19, with the first cases reported in December 2019 (Lu et al., 2020; Wu et al., 2020; Zhou et al., 2020). The disease expanded rapidly, and by March 12, 2020, COVID-19 was classified as a pandemic by the World Health Organization (WHO). As of January 31, 2021, the WHO has reported more that 100 million confirmed cases of COVID-19 and 2.2 million deaths globally (WHO, 2020a).

While most COVID-19 cases result in only mild disease, a substantial proportion of patients develop severe respiratory illness resulting in impaired gas exchange, hypoxia, need of supplementary oxygen and, in the most severe cases, mechanical ventilation (Chen et al., 2020; Ruan et al., 2020; Zhou et al., 2020).

Remdesivir and dexamethasone, have shown some impact on disease remission in large controlled trials in hospitalized COVID-19 patients and are now part of current standard of care (Beigel et al., 2020; Group et al., 2020) in many countries. Despite the benefits of these drugs, the morbidity and mortality in COVID-19 are still significant, particularly in moderately severe disease where it could be argued that no therapies have shown a consistent meaningful benefit. The need for safe, effective, and convenient COVID-19 drugs is likely to remain even after the launch of vaccine programs.

IMP treatment C21

C21 is a first-in-class, low molecular weight, orally available potent and selective AT2R agonist being developed for oral treatment of COVID-19 and fibrotic lung diseases such as idiopathic pulmonary fibrosis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of C21 is provided in the Investigator's Brochure (IB).

C21 has been evaluated in 3 completed phase 1 trials (C21-001-16, C21-002-16 and C21-003) and in 1 recently completed phase 2 trial in subjects with COVID-19 (VP-C21-006). In total, 134 subjects have been exposed to at least 1 dose of C21. Overall, C21 was well tolerated at doses up to 100 mg b.i.d. administered for up to 8 days.

The SARS-CoV-2 virus is known to bind to and enter target cells through angiotensin converting enzyme (ACE) 2, an integral component of the renin-angiotensin system (RAS) (Zhang et al., 2020). Within the RAS, the Angiotensin II type 1 receptor (AT1R) normally mediates the classical actions of Angiotensin II, including constriction of blood vessels, sodium retention and cell growth, while abnormal AT1R activation contributes to the pathogenesis of certain cardiovascular, renal and pulmonary diseases (de Man et al., 2012; Savoia & Schiffrin, 2006; Sumners et al., 2019). Conversely, activation of the AT2R causes dilatation of blood vessels and inhibition of inflammation and fibrosis, and is considered to be counter-regulatory to the negative effects of AT1R activation (Matavelli et al., 2015; Sumners et al., 2019).

While the AT2R is only expressed at low levels in most tissues in healthy adults (De Gasparo, 2002; Steckelings et al., 2005), it is highly expressed in alveolar type 2 progenitor cells in the adult human lung and can be upregulated during repair and regeneration (Akishita et al., 1999; Protein-Atlas). This, coupled with the belief that the RAS may play a key role in the development of COVID-19 led us to the view that C21 may have a role in the treatment of the disease by directly activating AT2R downstream of ACE2, thus by-passing any inherent negative effects in the infected state.

The safety and efficacy of C21 in subjects with COVID-19 were investigated in a randomized, double-blind, placebo-controlled, phase 2 trial (VP-C21-006). The trial included 106 adult subjects hospitalized with COVID-19, having a CRP between 50-150 mg/L and not in need of mechanical ventilation. The subjects were randomized to receive oral treatment with C21 (100 mg b.i.d., n=51) or placebo (n=56) for 7 days on top of standard of care. All subjects were followed up for 7 to 10 days after receiving the last investigational medicinal product (IMP) dose.

The treatment groups were well balanced regarding age (mean 52.6 years) and gender (75.5% males). Most patients had one or more coexisting medical conditions. Hypertension and overweight/obesity were more common in the C21 group compared with the placebo group, but there was no difference in the presence of diabetes mellitus. Supplementary oxygen supply at baseline was needed in 57.5% of the patients with no major difference between the treatment groups. Concomitant medication according to local standard of care was permitted in the trial. A vast majority of the patients received glucocorticoids, and most patients received antibacterial and antiviral compounds (remdesivir in 67.0%), with no major differences between the treatment groups.

Extended need for oxygen therapy was more frequent in the placebo group than in the C21 group. At Day 14, only one patient in the C21 group, compared to 11 patients in the placebo group, needed supplementary oxygen (p=0.003). This difference was already apparent at the end of the 7-day treatment period, when 27.5% of patients in the C21 group and 45.5% in the placebo group were in need of supplemental oxygen (p=0.055). The reduced need for extended oxygen supplementation indicates that treatment with C21 improves gas exchange at the alveolar level. Considering that the alveolar type 2 progenitor cells appear to be the only cells in the lungs that express the AT2R (Protein-Atlas) and are suggested to be the primary site for viral replication in

the distal airways (Szekely et al., 2020), C21 may restore respiratory function by acting directly on these cells.

There were 4 deaths in the trial, one in the C21 group and 3 in the placebo group. All deaths occurred in patients with progressive respiratory insufficiency and need for mechanical ventilation. One more patient in the placebo group deteriorated and developed need for mechanical ventilation.

CRP was initially selected as the primary endpoint because CRP has been reported to predict severe disease (Tan et al., 2020; Wang, 2020) and mortality (Ruan et al., 2020) in COVID-19. However, there was a rapid and profound decrease in CRP in both the C21 and the placebo group, most likely because the patients were treated with glucocorticoids which became part of standard of care at the time of trial initiation likely leading to no statistical difference in the primary endpoint CRP. Nevertheless, in the patients with more pronounced respiratory distress with need of supplementary oxygen at baseline, there was a small but significantly greater reduction of CRP in the C21 than in the placebo group.

There were 64 treatment-emergent AEs reported by 60.8% of the patients in the C21 group and 90 events reported by 67.3% of the patients in the placebo group. Most events were mild, and no event in either group was classified as related to trial treatment by the investigators. The most frequent AE was hyperglycemia, which occurred more frequently in the C21 group than in the placebo group. The level of hyperglycemia was predominantly mild and not reported as related to C21 by investigators.

Taken together, C21 on top of standard of care, including glucocorticoids and remdesivir, significantly improved respiratory function reflected by a reduced need for supplemental oxygen in hospitalized COVID-19 patients.

2.3. Benefit/Risk Assessment

COVID-19 can be a fatal disease, and the respiratory system is usually the worst affected bodily system. In general, hypoxemia is an accepted indication for intubation in COVID-19 patients (Voshaar et al., 2021). The results of the phase 2 trial in patients with COVID-19 (VP-C21-006) suggest a clinically relevant beneficial effect on the need for oxygen supplementation at a dose of 100 mg b.i.d. Overall, the safety profile of C21, as available from pre-clinical and phase 1 and 2 clinical trial data, is interpreted as favorable for the treatment of COVID-19.

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of C21 may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
IMP - C21		
Alopecia	Reversible alopecia was observed in subjects who received 200 mg b.i.d. for 8 days in a phase 1 trial, C21-003. Alopecia was not observed in the VP-C21-006 trial (51 subject treated with 100 mg b.i.d. for 7 days). Further information can be found in the IB.	No mitigation strategy implemented due to the severity of the COVID-19 disease in the trial population and the low risk of developing alopecia at the selected dose and treatment duration (100 mg b.i.d. for 14 days).
Drug-drug interactions	C21 is metabolized primarily by CYP3A4.	Exclusion of subjects treated with strong CYP3A4 inducers and/or with Warfarin.
	In vitro data show that a clinically relevant interaction with CYP enzymes (e.g., CYP2C9, CYP3A4 and CYP1A2) and efflux transporters (multi-drug resistance gene (MDR1) and breast cancer resistance protein (BCRP)) cannot be excluded.	The medical monitor and the DMC will monitor the extent of co-administration with CYP1A2, CYP3A4 and CYP2C9 substrates with a narrow therapeutic index and will inform the investigator if sub-optimal combinations occur. Exclusion of subjects treated with P-gp substrates with narrow therapeutic index, high dose BCRP sensitive substrates, and sulphasalazine or rosuvastatin.
Drug-food interactions	Exposure of C21 was substantially decreased under fed conditions as compared to fasted conditions indicating an interaction with food (VP-C21-003).	IMP will be administered in fasting conditions (see Section 5.3). Correct administration of IMP in relation to food intake will be monitored during the trial.

2.3.2. Benefit Assessment

Up to 20% of symptomatic individuals with COVID-19 will develop severe disease including acute respiratory distress syndrome and death. There is no cure, and interventions administered early in the course of the illness could prevent disease progression. Hypoxemia has been independently associated with in-hospital mortality, and medicines that improve respiratory insufficiency coupled with an effective vaccine, would have significant implications for the ability to end this pandemic (Xie et al., 2020).

Subjects randomized to active treatment in this trial may recover earlier or have a reduced risk of developing severe complications related to the COVID-19 disease. The option for out-patient treatment (following hospitalization) could reduce the strain on vital costly hospital resources.

All subjects will receive regular medical evaluations associated with their participation in the trial and will contribute to the development of new therapies in a disease area with a high unmet need.

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risk to subjects participating in this trial, the potential risks identified in association with C21 are justified by the anticipated benefits that may be afforded to subjects with COVID-19.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• Evaluate the efficacy of C21 versus placebo as add on to SoC on recovery in subjects with COVID-19.	• All-cause mortality up to Day 60
Key secondary	
	• Time to sustained hospital discharge up to Day 60. • Supplemental oxygen free days up to Day 29. • Proportion of subjects free of respiratory failure, defined as an 8-point ordinal scale score ≤5, at Day 15. • Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15.
Secondary	
• Evaluate the safety profile of C21 versus placebo as add on to SoC in subjects with COVID-19.	• AEs. • SAEs. • Changes in safety laboratory assessments. • Withdrawals due to AEs.
• Characterize the PK profile of C21 in subjects with COVID-19.	• PK parameters.
• Evaluate the efficacy profile of C21 versus placebo as add on to SoC in subjects with COVID-19.	• Proportion of subjects discharged from hospital and free of supplemental oxygen at Days 8, 22 and 29. • Proportion of hospitalized subjects on non-invasive, invasive mechanical ventilation, ECMO or supplemental oxygen use at Days 8, 15, 22, 29 and 60.

	• Proportion of subjects in each category of the 8-point ordinal scale at Days 8, 15, 22, 29 and 60. • Duration of hospitalization, including re-hospitalization, up to Day 60. • Proportion of subjects needing intensive care unit stay at Days 8, 15, 22, 29 and 60. • Duration of intensive care unit stay, including re-admission, up to Day 60. • Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29 and 60, and duration of use up to Day 60. • Proportion of subjects free of respiratory failure at Days 8, 22, 29 and 60, and respiratory failure free days up to Day 60. • All-cause mortality up to Days 8, 15, 22 and 29. • Change from baseline in SpO_2/FiO_2 at Day 15.
Exploratory	
• To explore the effect of C21 versus placebo as add on to SoC on inflammation.	• Change from baseline in CRP at Day 15.
• To explore the effect of C21 versus placebo as add on to SoC on lung injury.	• Change from baseline in lactate dehydrogenase (LDH) at Day 15.

Primary estimand

All-cause mortality up to Day 60 defined as the time to day of death from any cause assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects with no confirmed death before or at Day 60 being censored at day of withdrawal/Day 60 follow-up. The stratified log-rank test will be used to compare the treatments. The treatment difference will be expressed as a hazard ratio with 95% confidence intervals.

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Key Secondary estimands

Time to sustained hospital discharge up to Day 60; The first occurrence of a score ≤ 2 whereafter the score stays ≤2 for the remainder of the 60 days trial period, assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects who die prior to Day 60 being censored at Day 60 and subjects withdrawing due to other causes than death and not fulfilling the event being censored at the withdrawal day. The Kaplan-Meier difference in median time to sustained hospital discharge with 95% confidence intervals will be estimated.

Supplemental oxygen free days up to Day 29; For each subject the number of days between Day 1 and Day 29 with a score of ≤4 on the 8-point ordinal scale and with no documented use of COVID-19 related supplemental oxygen, assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects who die prior to Day 29 being given the value –1 day and trial withdrawals prior to Day 29 due to other causes than death and not possible to follow-up being imputed using multiple imputation including assessments from day 1 to day 29. The Hodge-Lehmann median estimated of the difference in days between treatments with 95% confidence intervals will be estimated.

Proportion of subjects free of respiratory failure at Day 15; The proportion of subjects with a score of ≤5 on the 8-point ordinal scale at Day 15, assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects who die prior to Day 15 considered as respiratory failure and trial withdrawals prior to Day 15 due to other causes than death and not possible to follow-up being imputed using multiple imputation including their baseline characteristics and last known status. The difference in proportions between treatments with 95% confidence intervals will be estimated.

Proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15; The proportion of subjects with a score of ≤2 on the 8-point ordinal scale and free of COVID-19 related supplemental oxygen use at Day 15, assessed for the intention-to-treat population with treatment as randomized, independent of treatment withdrawal or major protocol deviations according to the treatment policy, with subjects who die prior to Day 15 considered not discharged and trial withdrawals prior to Day 15 due to other causes than death and not possible to follow-up being imputed using multiple imputation including baseline characteristics and their last known status. The difference in proportions between treatments with 95% confidence intervals will be estimated.

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4. Trial Design

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, 2-arm, multicenter trial.

- Subjects hospitalized due to ongoing COVID-19 will be enrolled.
- The trial consists of 3 consecutive periods: a screening period of up to 48 hours, a 2-week IMP treatment period and a follow-up period of up to 7 weeks. Daily visits are required until discharge. Discharged subjects should return to the clinic for the Day 15 visit. Days 8, 22, 29 and 60 visits will be conducted as phone or video visits for all discharged subjects.
- The trial duration for an individual subject will not exceed 9 weeks.
- The trial will enroll a total of maximum 300 randomized subjects, 150 per arm (C21 100 mg b.i.d. or placebo for 14 days) according to a 1:1 randomization.
- Blinding will be performed with a matching placebo.
- Randomization occurs at visit 2 and will be stratified by:
    - Disease severity (based on the ordinal scale score at Day 1).
    - Region.
- An independent DMC will actively monitor data from the trial.

4.2. Scientific Rationale for Trial Design

The proposed clinical trial design is based on the guidance provided in the WHO COVID-19 therapeutic trial synopsis (WHO, 2020b), the FDA Guidance for Industry to support clinical development of drugs for the treatment and prevention of COVID-19 (FDA, 2020a), investigator and authority guidance.

The trial will enroll hospitalized subjects with a confirmed SARS-CoV-2 infection and on supplemental oxygen but not requiring mechanical invasive ventilation. There is a high unmet need for an efficacious treatment of COVID-19 in this population to halt respiratory failure and ultimately reduce mortality.

The primary endpoint is all-cause mortality up to Day 60. This endpoint is considered clinically relevant in the population studied and the timepoint of evaluation will ensure capturing the majority of events to assess a treatment response.

The primary endpoint is supported by data from the completed Phase 2 trial (VP-C21-006), in which C21 was associated with a numerical reduction in the mortality rate (one and three deaths in the C21 and placebo group, respectively). All deaths occurred in patients with progressive respiratory insufficiency and need for mechanical ventilation. One more patient in the placebo group deteriorated and developed need for mechanical ventilation.

The 8-point ordinal scale together with an assessment of supplemental oxygen use will be used for assessment of the key secondary endpoints. The ordinal scale is considered responsive to the selected COVID-19 population with respect to the treatment and course of the illness and such

scales have been used in the majority of phase 2 and 3 COVID-19 trials to date (Dodd et al., 2020). The 8-point ordinal scale is a composite measure of clinical improvement and/or survival assessed up to 60 days post randomization.

It has been demonstrated that there is a strong association between days on oxygen during the acute phase of COVID-19 and long-term recovery (Shah et al., 2021). In the Phase 2 trial, patients on C21 had a significantly lower use of supplementary oxygen therapy at end of treatment, only 1 out of 51 subjects in the C21 group was using supplemental oxygen at Day 14.

The WHO COVID-19 therapeutic trial synopsis recommends that subjects will be treated with IMP on top of SoC in (WHO, 2020b). Guidance on SoC is provided in Appendix 4 (see Section 10.4).

The placebo group and the blinding in the trial was implemented to minimize bias. The randomization will be stratified to ensure an equal distribution of active and placebo subjects by region and disease severity.

4.3. Justification for Dose

Subjects will be treated with oral 100 mg C21 or placebo b.i.d. for 14 days.

The results of the completed phase 2 trial in COVID-19 subjects (VP-C21-006) and of the phase 1 trial in healthy subjects (VP-C21-003) indicate an acceptable safety and tolerability profile for the 100 mg b.i.d. dose. The risks of C21 in adults are considered primarily related to reversible alopecia seen at the higher dose of 200 mg b.i.d. In the phase 2 trial in COVID-19 subjects (VP-C21-006) and the phase 1 trial (VP-C21-003), the 100 mg b.i.d. dose did not cause any hair loss (Further details can be found in the IB). Alopecia is therefore not considered to present any significant safety risk to subjects in this trial.

In the phase 1 trial (VP-C21-003), 100 mg b.i.d. dosing prolonged the duration of the plasma concentration at therapeutic relevant levels. After oral administration, C21 was rapidly absorbed. On Day 8, median t_{max} was 0.33 hours after each dose post-dose, and C21 was measurable in plasma until 4-6 hours after the first and second dose. Lower doses than 100 mg b.i.d. may not provide maximal efficacy benefit.

In the completed phase 2 trial (VP-C21-006) in COVID-19 subjects, treatment with 100 mg b.i.d. for 7 days, reduced the need for extended oxygen supplementation.

The recently completed phase 2 trial (VP-C21-006) indicates that C21 can prevent hypoxic critical illness and based on the course of the disease, there is a strong rational to extend the treatment duration from 7 to 14 days. Furthermore, 27% of subjects within the C21 arm were still in need of oxygen (vs 45% on placebo) at the end of the 7 days treatment, highlighting an opportunity to treat for a longer period to gain additional benefit, with the aim of returning patients to normoxia.

There is not enough evidence to treat beyond 14 days at this stage.

Based on the above, C21 will be administered at an oral dose of 100 mg b.i.d. for 14 days in the present trial.

4.4. End of Trial Definition

End of trial is defined as the date of the last visit of the last subject in the trial.

A subject is considered to have completed the trial if he/she has completed all periods of the trial including the Day 60 visit.

5. Trial Population

The trial will enroll adult subjects hospitalized due to SARS-CoV-2 infection.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the trial only if the following criteria are fulfilled:

Age

1. Age ≥18 years or the legal age of consent in the jurisdiction in which the trial is taking place at the time of signing the informed consent. (*Specific for India*; Age ≥18 at the time of signing the informed consent to ≤65 years.)

Type of Subject and Disease Characteristics

2. Hospitalized due to SARS-CoV-2 infection confirmed by a hospital-approved polymerase chain reaction (PCR) test, documented by either of the following:
    a. PCR positive in sample collected <72 hours prior to randomization (Visit 2); OR
    b. PCR positive in sample collected ≥72 hours and ≤7 days prior to randomization, documented inability to obtain a repeat sample AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
3. A score of 5 or 6 on the 8-point ordinal scale:
    a. Score 5: Hospitalized, requiring supplemental oxygen.
    b. Score 6: Hospitalized, on non-invasive ventilation or high-flow oxygen device.

Sex and Contraceptive/Barrier Requirements

4. Contraceptive use by men and women of childbearing potential consistent with local regulations regarding the methods of contraception for those participating in clinical studies and according to Appendix 3 (see Section 10.3).

Informed Consent

5. Written informed consent, consistent with International Council for Harmonization (ICH Good Clinical Practice (GCP) R2 and local laws, obtained before the initiation of any trial-related procedure.
6. Capable of giving signed informed consent as described in Appendix 1 (see Section 10.1.3) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Country specific

7. Specific for India: For subjects with an ordinal scale score of 5, moderate to severe COVID-19 disease confirmed by at an $SpO_2 \leq 93$ % or a respiratory rate ≥ 24/min on room air. Note: If a subject is on supplemental oxygen with SpO2 >93% and respiratory rate <24/min, but desaturation to ≤ 93 % or increase of respiratory rate to ≥ 24/min on lower supplemental oxygen or room air is documented during screening, the inclusion criterion is considered to be met.

5.2. Exclusion Criteria

Subjects are excluded from the trial if any of the following criteria apply:

Medical Conditions

1. Concurrent serious medical condition which in the opinion of the investigator constitutes a risk or a contraindication for the participation in the trial or that could interfere with the trial objectives, conduct or evaluation.
2. Known, active tuberculosis, active hepatitis B, C, or human immunodeficiency virus (HIV) infection (i.e., HIV with a CD4 count <500 cells/mm^3).
3. Moderate or severe impairment of hepatic function (e.g., Child-Pugh class B or C where alterations in the score components are not due to another underlying disease (see Section 8.4.5)).
4. Severe renal impairment (i.e., estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m^2).
5. COVID-19 symptom onset >21 days prior to screening (Visit 1).
6. Hospitalized due to COVID-19 for >72 hours at screening (Visit 1).
7. Invasive mechanical ventilation or ECMO within 72 hours of screening (Visit 1).
8. Expected need for invasive mechanical ventilation or ECMO in <48 hours in the opinion of the investigator.
9. Moderate to severe ARDS (e.g., same-day PaO_2/FiO_2 ≤200 mmHg; or SpO_2/FiO_2 ≤232 if arterial blood gas test is not available), if on non-invasive mechanical ventilation or high-flow oxygen.
10. Pregnant or breast-feeding female subjects.

Prior/Concomitant Therapy

11. Any previous and concurrent experimental treatment for COVID-19 that is not considered local SoC.
12. Treatment with the medications listed below within 1 week prior to screening (Visit 1) or anticipated need for such medication during the participation in this trial:
    a. Strong Cytochrome P450 (CYP) 3A4 inducers.
    b. P-glycoprotein (P-gp) substrates with narrow therapeutic index.
    c. High dose BCRP sensitive substrates.
    d. Warfarin.
    e. Sulphasalazine or rosuvastatin.

Prior/Concurrent Clinical Trial Experience

13. Current or previous participation in any other clinical trial where the subject has received a dose of IMP within 1 month or 5 half-lives of the IMP, whichever is longest, prior to screening (Visit 1).

Diagnostic Assessments

14. Positive pregnancy test (see Section 0).
15. Abnormal laboratory value at screening (Visit 1) indicating a potential risk for the subject if enrolled in the trial as evaluated by the investigator.

5.3. Lifestyle Considerations

In relation to IMP administration, subjects should adhere to meals and dietary restrictions regarding food intake:

- No food intake for 2 hours prior to taking the IMP.
- No food intake for 1 hour after taking the IMP.

5.4. Screen Failures

A screen failure occurs when a subject who consents to participate in the clinical trial is not subsequently randomly assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. Individuals who do not meet the criteria for participation in this trial (screen failure) must not be rescreened.

6. Investigational Medicinal Product and Concomitant Therapy

The IMP is the active (C21) or placebo treatment intended to be administered to a trial subject according to the trial protocol.

6.1. Investigational Medicinal Product Administered

Each subject will be randomized to receive treatment with the IMP (C21 or placebo). The IMP will be administered as a capsule for oral administration. Each subject will receive 4 capsules per day, divided in 2 doses given twice a day.

IMP will be administered in fasting conditions (see Section 5.3). C21 is an AT2R agonist. The drug substance is 3-[4-(1H-imidazol-1-ylmethyl)phenyl]-5-(2-methylpropyl)thiophene-2-[(N-butyloxylcarbamate)-sulphonamide] sodium salt supplied as a free form equivalent (eq.) 50 mg C21 oral capsule.

Table 1. Investigational Medicinal Product Administered

IMP Name	Active / C21	Placebo
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	52.3 mg pr capsule	Placebo
Dosage Level(s)	2 capsules, b.i.d.	2 capsules, b.i.d.
Excipients	Mannitol, Anhydrous colloidal silica, Magnesium stearate	Mannitol, Anhydrous colloidal silica, Magnesium stearate
Capsule	Vcaps® plus	Vcaps® plus
Route of Administration	Oral	Oral
Dosage description	Subjects will receive 100 mg C21 b.i.d. on Day 1 to Day 14.	Subjects will receive Placebo b.i.d. on Day 1 to Day 14.
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	IMP will be provided in a container. Each container will be labeled as required per country requirement.	IMP will be provided in a container. Each container will be labeled as required per country requirement.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP.
- Only subjects enrolled in the trial may receive IMP, and only authorized site staff may supply or administer IMP during hospitalization. Prior to dispensing, all IMP must be stored at 15 to 25 °C (59-77°F) in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- If a subject is discharged from the hospital prior to Day 15, IMP accountability will be performed, and the subject will be instructed to self-administer the remaining IMP at home. The subject must be instructed to store IMP at room temperature (15-25°C, 59-77°F). The IMP should be kept in the plastic container until intake, out of reach from children.
- In subjects where oral intake becomes a significant challenge e.g., during invasive mechanical ventilation or ECMO treatment, IMP will be administered as a dispersion, either orally or via a nasogastric or nasoenteral feeding tube. It may also include situations in which nasogastric or nasoenteral tube feeding may become required, such as non-invasive mechanical ventilation, high flow oxygen therapy and gastric/oesophagal discomfort. Route of administration will be collected in the eCRF.
- The subject should return all used and unused IMP at Visit 16 (Day 15) or at the EWD visit for subject withdrawing prior to Visit 16.
- The investigator and the pharmacy (if applicable) are responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information on preparation, handling, storage, and accountability are provided in the IMP handling manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind trial in which subjects, care providers, investigators, outcomes assessors, sponsor and CRO/vendor staff are blinded to IMP allocation i.e., intervention assignment. The interactive web response system will be programmed with blind-breaking instructions.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's intervention assignment unless this could delay emergency treatment for the subject. If a subject's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

Sponsor pharmacovigilance staff or the pharmacovigilance vendor appointed by the sponsor may unblind the intervention assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy. A blinding plan will describe any unblinded sponsor, or CRO/vendor staff during the conduct of the trial.

6.4. Investigational Medicinal Product Compliance

When subjects are randomized at the site, they will receive the IMP doses directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The IMP container number and trial

subject identification will be confirmed at the time of dosing by a member of the trial site staff other than the person dispensing the IMP.

During the hospitalization, the investigator or designee should investigate and document if the fasting criteria for the IMP (see Section 5.3) has been fulfilled.

If a subject is discharged from the hospital prior to Day 15 and self-administer the remaining IMP at home, IMP compliance and compliance with fasting criteria will be assessed at Visit 16 (Day 15) and documented in the source documents and the eCRF relevant form. Deviation(s) from the prescribed dosage regimen and fasting criteria should be recorded.

A record of the quantity of IMP dispensed to and administered by each subject must be maintained and reconciled with IMP and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

Dose modifications during the 14-day IMP treatment period are not allowed.

6.6. Continued Access to the Investigational Medicinal Product after End of Trial

There will not be continued access to the IMP after end of treatment (Day 15).

6.7. Treatment of Overdose

In this trial, any dose of C21 exceeding a total daily dose of 200 mg (i.e., 4 capsules of IMP) is considered an overdose.

Sponsor does not recommend any specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Evaluate the subject to determine, in consultation with the medical monitor, whether IMP treatment should be interrupted.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

Overdoses should be reported as an AE.

6.8. Prior and Concomitant Therapy

Concomitant therapy is defined as any medication or vaccine (including over-the-counter, prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the subject is receiving at the time of enrollment or receives during the trial.

SoC for COVID-19 as described in Appendix 4 should be applied during the trial.

All concomitant therapy and prior therapy taken up to 4 weeks prior screening (Visit 1) should be recorded. The investigator must obtain information on medications and therapies for the COVID-19 related infections for each subject.

Other relevant prior therapy as judged by the investigator will be collected and recorded.

Concomitant therapy and prior therapy must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

COVID-19 vaccination is allowed prior to screening (Visit 1) and after the end of the IMP treatment period (Day 15). Vaccination for COVID-19 during the IMP treatment period is prohibited. COVID-19 vaccinations should be recorded in the eCRF. Treatment with the following prohibited medication is not allowed from 1 week prior to screening (Visit 1) and until Day 15 (Visit 16):

a. Strong Cytochrome P450 (CYP) 3A4 inducers
b. P-glycoprotein (P-gp) substrates with narrow therapeutic index
c. High dose BCRP sensitive substrates
d. Warfarin
e. Sulphasalazine or rosuvastatin

Strong Cytochrome P450 (CYP) 3A4 inducers, P-glycoprotein (P-gp) substrates with narrow therapeutic index and high dose BCRP sensitive substrates considered prohibited medication include drugs listed in the FDA tables of substrates, inhibitors and inducers for drug development and drug interactions (FDA, 2020b).

7. Discontinuation of Investigational Medicinal Product and Subject Discontinuation/Withdrawal

Discontinuation of specific sites or of the trial are detailed in Appendix 1 (see Section 10.1).

7.1. Discontinuation of Investigational Medicinal Product

A subject should be withdrawn from the IMP treatment if it in the opinion of the investigator is medically necessary or if it is the wish of the subject.

If IMP treatment is discontinued, the date of last IMP administration and the date and reason for treatment withdrawal should be reported in the eCRF. If a subject is removed from treatment because of an AE, the reason for treatment withdrawal should always be stated as 'adverse event' irrespective of whether this was the investigator's or the subject's decision.

If IMP treatment is discontinued, the investigator should make all efforts to ensure that the subject will remain in the trial and ensure that the subject attends the remaining visits in the trial.

IMP treatment should be discontinued in case of drug induced liver injury according to criteria specified in FDA guidance (FDA, 2009), moderate or severe impairment of hepatic function (e.g., Child-Pugh class B or C where alterations in the score components are not due to another underlying disease (see Section 8.4.5)), or severe renal impairment (i.e., estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m2).

7.1.1. Temporary Discontinuation

There are no specific criteria for temporary discontinuation of IMP treatment. If temporary discontinuation of IMP is required according to investigator's judgement, the date and reason for a temporary discontinuation should be reported in the eCRF. If the subject is still within the treatment period of the trial when a temporary discontinuation is no longer required, IMP treatment can be restarted.

7.2. Subject Discontinuation/Withdrawal from the Trial

- A subject may withdraw from the trial at any time at his/her own request i.e., withdrawal of consent.
- At the time of discontinuing from the trial, if possible, an EWD visit should be conducted, as described in the SoA.
- The subject will be permanently discontinued from the IMP at the time of withdrawal from the trial.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

7.3. Lost to Follow up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the clinic for a required trial visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial.

8. Trial Assessments and Procedures

- Trial procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor or designee immediately upon occurrence or awareness to determine if the subject should continue or discontinue IMP.
- Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (e.g., PCR tests for SARS-CoV-2 collected less than 3 days prior to Visit 2 (or less than 7 days prior to Visit 2 in case of documented inability to obtain a repeat sample and progressive disease suggestive of ongoing SARS-CoV-2 infection)) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the trial, including any extra assessments that may be required, will not exceed 130 mL.

8.1. Screening Assessments

Planned timepoints for all screening assessments are provided in the SoA. Screening procedures may be done over 1 to 2 calendar days.

8.1.1. Demographics

Demographic and baseline characteristics will be obtained. This following information will be collected:

- Age at screening
- Race and ethnicity
- Sex
- Height
- Body weight

8.1.2. Medical History

All current medical conditions and relevant previous medical conditions according to investigator judgement should be recorded.

The medical history should include the following information:

- Date of onset of COVID-19 signs and symptoms.
- Date of COVID-19 diagnosis (defined as sample date for positive COVID-19 PCR test).
- History of chronic medical conditions including chronic supplemental oxygen requirement prior to onset of COVID-19 signs and symptoms.
- History of previous COVID-19 diagnosis and serology results (if relevant and known).

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1. 8-point Ordinal Scale

The clinical status of COVID-19 is scored at each visit according to the 8-point ordinal scale (Beigel et al., 2020), which is an investigator evaluation of the clinical status at the first assessment of a given trial day. The clinical status of COVID-19 according to the 8-point ordinal scale must further be scored at the time of hospital discharge. For subjects hospitalized between Day 29 (Visit 31) and Day 60 (Visit 32), the clinical status of COVID-19 should be scored each time a change in clinical COVID-19 status is seen and until hospital discharge.

The 8-point ordinal scale is as follows:

1.	Not hospitalized, no limitations on activities
2.	Not hospitalized, limitation on activities and/or requiring home oxygen
3.	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4.	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19-related or otherwise)
5.	Hospitalized, requiring supplemental oxygen
6.	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7.	Hospitalized, on invasive mechanical ventilation or ECMO
8.	Death

A subject re-admitted to the hospital for a non-COVID-19 related reason should be considered not hospitalized when scoring the clinical status of COVID-19 on the 8-point ordinal scale.

8.2.2. Supplemental Oxygen

Any daily need for supplemental oxygen will be recorded at each visit from screening (Visit 1) to Day 29. This will include use of supplemental oxygen during hospitalization and at home.

8.2.3. Oxygen Saturation

- Resting peripheral capillary oxygen saturation (SpO_2) will be performed as outlined in the SoA.
- SpO_2 recording should be preceded by at least 5 minutes of rest for the subject in a quiet setting.
- SpO_2 will be recorded up to 2 times with a 5-minute interval between the measurements.
- Supplemental oxygen flow rate (L/min), oxygen delivery device, FiO_2, airway pressure, if applicable, must be assessed at the time of measuring SpO_2.

8.3. Survival and Hospitalization

Data on survival, hospital discharge and hospital re-admissions will be collected at each visit from Day 2 (Visit 3) to Day 60 (end-of-trial). Information on the hospital setting, including intensive care unit (ICU), high flow oxygen device use, ventilator use (Non-invasive, Invasive or ECMO) will be collected.

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.4.1. Physical Examinations

- Physical examinations will be performed as outlined in the SoA (see Section 1.3).
- The physical examination will include assessments of the respiratory and cardiovascular systems. Other systems will be assessed per investigator judgment.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Each body system will be reported as “normal” or “abnormal”. Any clinically significant abnormalities prior to initiation of IMP should be specified and recorded as medical history. New clinically significant abnormalities occurring after initiation of IMP should be reported as AEs.

8.4.2. Vital Signs

- Body temperature, pulse rate, respiratory rate and blood pressure will be measured as outlined in the SOA (see Section 1.3).
- Blood pressure, respiratory rate and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).

- Any clinically significant abnormalities prior to initiation of IMP should be specified and recorded as medical history. New clinically significant abnormalities occurring after initiation of IMP should be reported as AEs.

8.4.3. Electrocardiograms

- 12-lead electrocardiograms (ECGs) will be obtained as outlined in the SoA (see Section 1.3) using local ECG equipment that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.
- Historical 12-lead ECGs are acceptable if ≤2 days old at the time of screening (Visit 1).
- The ECG assessment will be reported as “normal” or “abnormal”. Any clinically significant abnormalities should be specified and recorded as medical history.

8.4.4. Clinical Safety Laboratory Tests

- Blood and urine samples for clinical safety laboratory tests will be collected as outlined in the SoA (see Section 1.3). Samples collected at screening (Visit 1) will be analyzed using local laboratories and used to confirm eligibility for participation in the trial.
- Day 1 (Visit 2), samples will be collected before IMP administration.
- Samples collected at all other visits will be analyzed by the central laboratory.
- If needed due to special circumstances e.g., delays in turn-around time due to COVID-19, blood samples may be analyzed locally after sponsor approval.
- The tests detailed in Table 2 will be performed.

Table 2. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count (thrombocytic particle concentration) Hemoglobin Hematocrit (erythrocyte volume fraction) Mean corpuscular volume (MCV)	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen (BUN) Glucose, fasting Potassium Sodium Calcium Ferritin Prothrombin time (PT) International Normalized Ratio (INR) activated partial thromboplastin time (aPTT)	AST Alanine transferase (ALT) Alkaline phosphatase (ALP) Albumin Total and direct bilirubin Serum creatinine eGFR CRP LDH
Routine urinalysis	• pH, glucose, protein, ketones, bilirubin, urobilinogen, and specific gravity by dipstick • Microscopic examination (per investigator judgment)	
Pregnancy testing	• Highly sensitive urine or serum human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)	

- Investigators must review of each laboratory safety report. Any clinically significant abnormalities at screening (Visit 1) or Day 1 (Visit 2) will be reported as medical history. New clinically significant abnormalities after Day 1 (Visit 2) should be reported as AEs.

8.4.5. Hepatic Impairment

In subjects with hepatic impairment, the grade of impairment will be assessed by the investigator prior to randomization and as needed during the trial using the Child-Pugh system (FDA, 2003). For subjects assessed using the Child-Pugh system, it is important that impaired hepatic function, not another underlying disease, is the cause of alterations in the Child-Pugh components (bilirubin, albumin, prothrombin time, encephalopathy, and ascites). Scoring will be performed according to Table 3 and the classification will be based on the total score;

- Class A (mild): 5 or 6 points

- Class B (moderate): 7 to 9 points
- Class C (severe): 10 to 15 points

Table 3. Child-Pugh System

	Points scored for observed findings		
	1	**2**	**3**
Encephalopathy grade[1)]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Total bilirubin[2)]	<2 mg/dL (<34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	>3 mg/dL (>51.3 µmol/L)
Serum albumin[2)]	>3.5 g/dL (>35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time, sec prolonged (or INR as below) INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1) Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

2) If using results from the central laboratory for calculating the scores, the alternative units may have to be considered

8.4.6. Pregnancy Testing

Women of childbearing potential will undergo pregnancy tests (urine dip-sticks or serum if required by local regulations) at the screening and Day 15 visits or at the EWD visit if the subject is withdrawn prematurely. The outcome of the test will be reported as “positive” or “negative” in the eCRF. If the urine pregnancy test is positive, a blood pregnancy test will be performed to confirm positive pregnancy.

Women of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or post-menopausal defined as 12 months of amenorrhea) (see Section 10.3).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject’s participation in the trial.

8.4.7. SARS-CoV-2 Variant

Oropharyngeal swabs will be collected as outlined in the SoA (see Section 1.3). A central laboratory will determine the SARS-CoV-2 variant.

8.4.8. New Infections

Information on new infections (viral and non-viral) should be reported as AEs. Information should preferably include the site of infection and source of culture.

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 2 (see Section 10.2).

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the IMP or trial procedures, or that caused the subject to discontinue the IMP or trial (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2 (see Section 10.2).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from signing of the ICF until Day 29 at the timepoints specified in the SoA (see Section 1.3). SAEs will further be collected until Day 60. All AEs are followed until they have reached a final outcome (see Section 10.2) or the subject's participation in the trial ends, whichever comes first.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours after SAE awareness, as indicated in Appendix 2 (see Section 10.2). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Information on SAEs must be entered in the eCRF.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, and he/she considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor regardless of the time that has elapsed (post-trial events).

8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (see Section 7.3). Further information on follow-up procedures is provided in Appendix 2 (see Section 10.2).

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification – within 24 hours of SAE awareness - by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of the IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)s/ independent ethics committee (IEC)s, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it in the investigator site file and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of IMP and until the end of trial visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.
- Any posttrial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor (see Section 8.5.4). While the investigator is not obligated to actively seek this information in former trial subjects/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.6. Pharmacokinetics

- PK data will be collected at a pre-selected number of trial sites in a subgroup of approximately 10 subjects.
- Blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of C21 as specified in the SoA (see Section 1.3). At Day 1 (Visit 2), blood samples will be collected before the first IMP administration and 30 minutes, 1, 2, 3, 4 and 6 hours after the IMP administration.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample as well as the date and time of the IMP administration will be recorded.
- PK data will not be reported to the trial sites, sponsor or blinded CRO/vendor staff until the trial has been unblinded.
- The individual plasma concentration data, and the actual time for IMP administration and blood sampling will be used throughout the analyses.
- All C21 plasma concentration data collected in this trial can be included in population PK and population PK/PD analyses with the objective of exploring the impact of covariates (e.g., body weight and age) on the PK of C21, or the relationship between the C21 exposure and selected efficacy and safety endpoints. Any population PK and population PK/PD analyses will be reported separately.
- From the plasma C21 concentration data analysis, the following PK variables will be derived using non-compartmental analysis:
  - C_{max} - Observed maximum plasma concentration of C21.
  - t_{max} - Time to reach C_{max} following IMP administration.
  - $AUC_{(0-6)}$ - Area under the plasma concentration curve from time zero to 6 hours.
  - AUC_{last} - Area under the plasma concentration-time curve from time zero to the last quantifiable concentration.
  - $AUC_{(0-inf)}$ - Area under the plasma concentration-time curve from time zero extrapolated to infinity.
  - $t_{½}$ - Apparent terminal half-life.
  - C_6 - Actual plasma concentration of C21 at 6 hours after IMP administration.

8.7. Genetics

Genetics are not evaluated in this trial.

8.8. Biomarkers

- Plasma samples will be collected to investigate a range of laboratory parameters as potential biomarkers of inflammation, fibrosis, and viral activity including serology.

Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites.

- Sponsor may store and analyze samples for up to 2 years after the end of the trial to achieve trial objectives.
- Biomarker results will be reported separately from the clinical trial report.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this trial.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters will be evaluated in terms of days hospitalized and days at intensive care unit. Additional analyses may be conducted outside of the clinical trial report.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to unblinding, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The aim of this trial is to show superiority of C21 over placebo regarding selected efficacy measures. The null hypothesis to be tested for each endpoint will be that there is no difference between C21 and placebo, against the alternative hypothesis that C21 is better than placebo. All tests will be done using 2-sided alternatives.

9.1.1. Multiplicity Adjustment

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in following hierarchical order; all-cause mortality up to Day 60, time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, proportion of subjects free of respiratory failure at Day 15, and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15. This means that statistically significant results for the comparison in the higher rank are required to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Subject Analysis Set	Description
Intention to treat (ITT) analysis set	All randomized subjects. Subjects will be included in the analyses according to the intervention they were randomized to.
Per protocol (PP) analysis set	All subjects in the ITT set without major protocol deviations deemed to have an impact on efficacy readouts. In addition, subjects who prematurely discontinued IMP during the treatment period but continued with data collection in the trial will also be excluded from the PP. Subjects withdrawn from the trial unrelated to trial participation due to extraordinary circumstances (for example subjects lost-to follow up due to unstable geopolitical situation) may also be excluded from the PP set (further specified in the SAP). Subjects will be included in the analyses according to the intervention they were randomized to.
Safety analysis set	All randomized subjects who are exposed to IMP. Subjects will be analyzed according to the actual intervention received.

Subject Analysis Set	Description
PK analysis set	All subjects randomized to C21, exposed to IMP and with at least one post-IMP blood sample with quantifiable C21 concentration collected. Participants may be excluded from the PK analysis population if they have important protocol deviations that are judged to significantly impact the PK analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

All tests will be 2-sided at a 5% significance level.

Baseline will be defined as the last non-missing assessment obtained prior to first IMP administration.

Stratification will be done based on baseline disease severity, that is the score on the ordinal scale at baseline (5 or 6), and region (North America, South and Central America, Europe, Africa, or Asia). The actual stratification will be used as factors in the statistical analysis, subjects included in wrong stratum at randomization will be moved to their correct strata belonging in the analyses. Due to small strata, the regions may be merged; details of this will be given in the SAP.

Continuous variables will be summarized using (arithmetic) means, standard deviation (SD), median, minimum, and maximum value, categorical variables will be summarized using numbers and percentages. For variables with an expected skew distribution, geometric means, and coefficient of variation (CV) will be used instead of arithmetic means and SD.

The ITT analysis set is used to analyze endpoints related to the efficacy objectives, the PP analysis set will be used for sensitivity analyses related to efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety. PK data will be presented using the PK analysis set.

All data regarding subject characteristics, efficacy and safety will be listed.

9.3.2. Primary Endpoint/Estimand Analysis

The primary endpoint, all-cause mortality up to Day 60, will be defined as the time to day of death from any cause within Day 1 to Day 60 follow-up. Subjects without event will be censored at Day 60 follow-up. Withdrawn subjects without event will be censored at day of discontinuation. Treatment groups will be compared using a stratified log-rank test adjusting for treatment, baseline disease severity (score on ordinal scale at baseline) and region. The size of the treatment effect will be given as a hazard ratio with 95% confidence intervals. Analysis will be illustrated using a Kaplan-Meier plot.

As a sensitivity analysis, the proportion of subjects with death up to Day 60 will be compared between treatment groups using a logistic regression model adjusting for treatment, baseline disease severity and region. The estimated difference between treatment groups will be expressed as a difference in proportions based on the fitted logistic regression model. The delta

method will be used to calculate the standard error for the difference and the associated 95% confidence interval (Ge et al., 2011). In addition, the raw proportions per treatment group will be given.

The ITT analysis set will be used for primary analysis and sensitivity analysis will be performed using the PP analysis set, subjects will be included as randomized. All collected data post-treatment will be used to assess the status of the subjects. Impact of subjects not properly being followed-up regarding status at Day 60 follow-up will be investigated.

9.3.3. Secondary Endpoints Analysis

The ITT analysis set will be used for primary analysis and the PP analysis set will be used for sensitivity analysis of key secondary endpoint. Subjects will be included in analyses as randomized. The key secondary endpoints will be time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, the proportion of subjects free of respiratory failure at Day 15 and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15.

The key secondary endpoints will be tested in a pre-specified hierarchical order following the test of the primary endpoint. Other secondary endpoints will be tested independently without adjustment for multiple tests.

The first key secondary endpoint, time to sustained hospital discharge, will be defined as the first occurrence of a score of ≤2 on the ordinal score within Day 1 to Day 60, after which the score must stay ≤2 for the remainder of the trial (no re-hospitalization related to COVID-19). Treatment groups will be compared using a stratified log-rank test adjusting for treatment, baseline disease severity and region. The size of the treatment effect will be given as a hazard ratio with 95% confidence intervals. Analysis will be illustrated using a Kaplan-Meier plot and, if a sufficient number meets the endpoint, the median time to hospital discharge will be estimated with 95% confidence intervals for each treatment group. Subjects who die prior to Day 60 will be censored at Day 60 and trial withdrawals prior to Day 60 due to other causes than death without fulfilling the event will be censored at day of withdrawal. Subjects still in trial but not discharged from hospital at Day 60 will be censored at Day 60.

The second key secondary endpoint, oxygen supplemental free days up to Day 29, will be defined as the number days for each subject with a score of ≤4 and no use of COVID-19 related supplemental oxygen. Treatment groups will be compared using the Wilcoxon rank-sum test and the treatment difference will be expressed as the Hodge-Lehmann difference in median number of days with 95% confidence intervals. All collected data post-treatment will be used. Subjects who die prior to Day 29 will be given the value of –1 day in the analysis and trial withdrawals prior to Day 29 due to other causes of death will be imputed (for each day) using multiple imputation including status for all of days 1 - 29. The cumulative distribution functions will be plotted to visualize the differences between treatment groups.

The third key secondary endpoint, subjects free of respiratory failure, will be defined as subjects with an ordinal scale score of ≤5 at Day 15. Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region. All collected data post-treatment will be used to assess the scores. Subjects who die prior to Day 15 will be considered in respiratory failure and trial withdrawals prior to Day 15 due to other causes than death and not possible to follow-up will be imputed using multiple imputation taking subjects

baseline characteristics and last known status into account. The adjusted proportions as calculated from (Ge et al., 2011) and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

The fourth key secondary endpoint, proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15, will be defined as subjects with a score of ≤2 on the ordinal scale and free of COVID-19 related supplemental oxygen use at Day 15. Treatment groups will be compared using a logistic regression model adjusting for treatment, baseline disease severity and region. All collected data post-treatment will be used to assess the scores. Subjects who die prior to Day 15 will be considered not discharged and trial withdrawals prior to Day 15 due to other causes than death and not possible to follow-up will be imputed using multiple imputation taking subjects baseline characteristics and last known status into account. The adjusted proportions as calculated from (Ge et al., 2011) and the statistics (treatment difference, SE and CI) following multiple imputation will also be presented. The ITT will be used for the analysis. The number of responders/non-responders will also be presented (these will be the non-imputed values).

Other endpoints assessing proportion of subjects will be compared using similar logistic regression models as for the primary endpoint with the treatment effect expressed as a difference in proportions. Death prior to endpoint readout will be handled as worst case, that is subject will be assumed to be in mechanical ventilator need or to be in oxygen need or not to have fulfilled an improvement of 1 or 2 units. Subjects in ventilator need at readout will be considered in oxygen need.

Other endpoints assessing time to event will be compared using the stratified log-rank test similar to time to sustained discharge with similar imputations for missing data.

Endpoints assessing duration of event will be compared between treatments using the Wilcoxon rank sum test, with similar imputations for missing data. All days up during which the subject is hospitalized for COVID-19 will be used for computation with imputation of days as being in event for subjects in ventilator care and for subjects with death as outcome. For duration of ICU stay, subjects with no ICU stay will be given the value 0 days in the analysis and subjects with death as outcome will be considered in ICU from time of death until end of observational period.

The change from baseline to Day 15 in SpO_2/FiO_2 will be compared between treatment groups using an analysis of covariance (ANCOVA) model with treatment, baseline disease severity and region as factors and the baseline SpO2/FiO2 as covariate. The adjusted mean difference between treatments will be given together with 95% confidence intervals and associated 2-sided p-value.

9.3.4. Exploratory Endpoint Analysis

The change in CRP and LDH from baseline up to Day 15 will be compared between treatment groups with ANCOVA models adjusting for treatment, baseline disease severity and region as factors and baseline as a covariate. Model for CRP and LDH will be multiplicative, that is data being log-transformed prior to analysis and the result back-transformed to the linear scale.

9.3.5. Safety Analyses

Safety analysis will be based on the safety set.

AEs will be analyzed using quantitative and qualitative measures. Treatment-emergent AEs (TEAEs) will be summarized by treatment group for all AEs, related AEs, SAEs, deaths, AEs leading to discontinuation of blinded IMP treatment or to withdrawal from trial, AEs of different severity and AEs of different chronicity. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term for each treatment group.

Laboratory data will be summarized by each visit including change from baseline. The number of high, low, and normal values for each continuous parameter, and the normal and abnormal values for each categorical parameter, will be summarized for change over time using shift tables.

Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure) will be summarized by each visit including change from baseline. Abnormalities find at physical examination will be summarized by visit. Outcome of pregnancy tests will be listed.

9.3.6. Other Analyses

The subject flow including total number of screened subjects, number of randomized subjects, completers, withdrawn subjects (including reason for withdrawal) and subjects included in each of the analysis sets will be summarized by treatment group and for the total.

The number of subjects with major protocol deviations will be summarized by category of violation and by treatment group including subset of major protocol deviations leading to exclusion from the per-protocol analysis set.

Demographic and baseline characteristics will be summarized using descriptive statistics for each treatment group and for the total number of randomized subjects. Medical history will be coded using MedDRA and summarized by system organ class and preferred term for each treatment group. Prior medications will denote medications used prior to first dose of IMP independent of if stopped at randomization or not. Concomitant therapy will denote medications started prior to but continuing after randomization or medications with a start date at or after the randomization date. Prior and concomitant therapy will be summarized separately by Anatomical Therapeutic Chemical levels 2 and 4.

Several sensitivity analyses will be performed on the primary and key secondary endpoints regarding choice of population (PP population) and choice of imputation for missing data. Specifically tipping point analyses will be performed on key secondary endpoints based on the ordinal scale.

Subgroup analyses of the primary and key secondary endpoints will be made to assess consistency of the intervention effect across at least the following subgroups:

- Age group: <65 vs ≥65 years
- Sex: female vs male
- Baseline disease severity (8-point ordinal scale 5 or 6 at Day 1)

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White or Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (North America, South and Central America, Europe, Africa, or Asia)
- Presence of risk factors for severe COVID-19 (Yes, No)

If the number of subjects is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the trial. Further details on the statistical analysis will be provided in the SAP.

9.4. Interim Analysis

No formal interim analysis will be performed. The DMC will review the safety results after the first 150 randomized subjects have completed trial up to Day 15.

9.5. Sample Size Determination

The sample size is based on the all-cause mortality up to Day 60. For the placebo (SOC) group, the proportion of subjects dead at Day 60 is estimated to 10% (Marconi et al., 2021).

With 150 evaluable subjects per trial group, there will be an 80% power to detect a difference between C21 and placebo if the proportion of subjects dead at Day 60 in the C21 group is 2.5% (corresponding to a HR of 0.24). In this calculation, a 5% withdrawal rate has been assumed. For the actual detection limit (corresponding to 50% power), if 15 subjects die in the placebo group, significance will be seen if at most 6 subjects die in the C21 group.

This assumes using a 2-sided test at a 5% significance level. Analysis will be by intention-to-treat; thus, all randomized subjects should be accounted for in the statistical evaluation.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
    - Applicable ICH GCP guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes except for changes necessary to eliminate an immediate hazard to trial subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial subjects.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the trial, including the risks and benefits, to the subject and answer all questions regarding the trial.

- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (US only), local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or trial center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be reconsented, as applicable, to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the subject.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that his/her medical records may be directly examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

An independent DMC will be established. The functions and responsibilities of the DMC will be described in a DMC charter.

Throughout the duration of the trial, the DMC will evaluate all SUSARs on an ongoing basis. The DMC is scheduled to meet twice during trial conduct, to review unblinded safety data from the trial after data collection for 15 days on the first 25% of randomized subjects, and to review safety and efficacy data after data collection for 15 days on the first 50% of randomized subjects. In addition, the DMC members may call for an *ad hoc* safety review meeting at any time during the trial. This may include a review of unblinded safety data after data collection for 15 days on the first 75% of randomized subjects. The DMC will provide appropriate written recommendations to the sponsor regarding trial continuation, protocol modifications or trial suspension. The DMC will operate unblinded and independent from all sites, CRO, vendor and sponsor staff involved in the conduct of the trial.

10.1.6. Dissemination of Clinical Trial Data

Information about the clinical trial and tabular trial results will be posted on the US National Institutes of Health's website www.clinicaltrials.gov and on the European Union Drug

Regulating Authorities Clinical Trials Database (EudraCT) prior to first subject first visit and after trial completions. Information about the clinical trial may also be posted on other governmental webpages according to local regulations.

10.1.7. Data Quality Assurance

- All subject data relating to the trial will be entered into electronic CRFs unless transmitted to the sponsor or designee electronically (Central laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guideline provided separately to sites.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the sponsor risk management plan to identify systematic issues that can impact subject safety and/or reliability of trial results. These predefined QTLs will be monitored during the trial, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical trial report.
- Monitoring details describing strategy, including definition of trial critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this trial, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents containing source data provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be

explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in the monitoring manual.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Trial and Site Start and Closure

First Act of Recruitment

The trial start date is the date on which the clinical trial will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the trial start date.

Trial/Site Termination

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

For trial termination:

- Discontinuation of further IMP development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

- The primary publication should be published by the sponsor prior to any other investigator-initiated publications, manuscripts, abstracts, or presentations.
- The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of IMP, whether or not considered related to the IMP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after IMP administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant therapy. Overdose to be reported as an AE/SAE. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

10.2.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.2.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- AEs will be collected from signing the ICF. AEs occurring after first IMP intake will be considered treatment-emergent adverse events (TEAEs) in the statistical analysis.
- A pre-existing medical condition should be reported as an adverse event if the condition increases in severity (e.g. from mild to moderate).
- At each visit the subject should be asked about AEs in an objective manner, *e.g.*: "Have you experienced any problems since the last visit?".
- Only medically qualified personnel (investigators) must assess AEs.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the SAE form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- All AEs should be followed until they have reached a final outcome (Recovered/resolved, recovering/ resolving, recovered/resolved with sequelae) or the subject's participation in the trial ends, whichever comes first.
- SAEs and non-serious AEs considered related to IMP treatment should be followed on a regular basis according to the investigator's clinical judgment until a final outcome has been established.
- The outcome "recovering" can be used as the final outcome for events that are stabilized (in essence no further worsening is expected) and expected by the investigator to resolve over time.

  The outcome "not resolved" can be used as the final outcome for events that are not expected to resolve over time (e.g. cancer).

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to one of the following categories:

- Mild: Awareness of symptoms, sign, illness, or event that is easily tolerated.
- Moderate: Discomfort sufficient to interfere with usual activities.
- Severe: Incapacitating with inability to work or undertake further normal activities.

Note the distinction between seriousness and severity: The term severe is used to describe the intensity of the event and a severe event is not necessarily serious. A severe headache would probably not constitute a SAE whilst a mild myocardial infarction likely would constitute a SAE. The seriousness criteria serve as a guide for defining regulatory reporting obligations.

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality when new follow-up information is available and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- The relationship will be characterized using the following causality ratings:
    - Related: There is a reasonable possibility that the AE was caused by the IMP treatment. There is a reasonable time relationship to IMP treatment intake. The AE cannot be explained by disease or other drugs. There may or may not be information about de-challenge or re-challenge. Disappearance of the AE upon de-challenge supports this category. Reappearance upon re-challenge is strongly supportive.

- Not related: There is no reasonable possibility that the event was caused by the IMP. The temporal relationship to drug administration makes a causal relationship improbable or other drugs or underlying disease or conditions provide plausible explanations.
- Not applicable: This assessment can be used e.g., in cases where the subject did not receive any treatment with IMP

Outcome

The Investigator is obliged to record the most appropriate outcome using the following categories:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved/ongoing
- Recovered/resolved with sequelae
- Fatal
- Unknown

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to the sponsor or designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor or designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the trial is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a trial subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken

offline, then the site can report this information on a paper SAE form or to the sponsor or designee by telephone.

- Contacts for SAE reporting can be found in the Safety Management Plan provided to the sites.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Requirements

Contraceptive use by men and women must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies and be according to the following gender specific requirements:

1. Male subjects are eligible to participate if they agree to the following during the IMP treatment period and for at least 2 weeks after the last dose of IMP:

    i. Refrain from donating fresh unwashed semen

    AND

    ii. Must agree to use contraception/barrier as detailed below

    iii. Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a woman) of childbearing potential (WOCBP) who is not currently pregnant

    iv. Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person

2. Female subjects are eligible to participate if she is not pregnant or breastfeeding, and the following conditions applies:

    i. Is a woman of nonchildbearing potential (WONCBP) as defined in section 10.3.2. Contraception and Barrier Guidance.

    ii. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency. Contraception and Barrier Guidance during the IMP treatment period and for at least 2 weeks after the last dose of IMP and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of IMP.

    iii. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) before the first dose of IMP (see Section 0).

    iv. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

    v. Additional requirements for pregnancy testing during and after IMP treatment (see Section 8.5.5).

    vi. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.3.2. Definitions

Women in the following categories are considered WOCBP (fertile):

- Following menarche
  - From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
  - Permanent sterilization methods (for the purpose of this trial) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial entry.

  Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

  - If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of IMP treatment, additional evaluation should be considered.

Women in the following categories are considered WONCBP:

- Premenopausal female with permanent infertility due to one of the following:
  a. Documented hysterectomy
  b. Documented bilateral salpingectomy
  c. Documented bilateral oophorectomy
  d. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial eligibility.

  Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- Postmenopausal female
  a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     i. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt should not be considered to be in a postmenopausal state.

10.3.3. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this trial. Male condom and female condom should not be used together (due to risk of failure from friction).

10.4. Appendix 4 Standard of Care for COVID-19

All subjects receiving IMP will also receive SoC for COVID-19, which may include:

- Oxygen administration to maintain oxygen saturation of 90 % to 96 %, including supplemental oxygen (low flow or high flow), non-invasive or invasive mechanical ventilation or ECMO
- Frequent clinical assessments of neurological, pulmonary, cardiac, gastrointestinal, and urinary status as required depending on clinical status
- At least daily monitoring of vital signs (heart rate, blood pressure, body temperature, respiratory rate and oxygen saturation (SpO_2))
- Telemetry monitoring to evaluate hearth rhythm and rate
- Diet as tolerated to satisfy nutritional needs
- Mobilization of the subject and rotation to prone positioning of ventilated subjects
- Treatment for COVID-19 symptoms including antibiotics, cough suppressant / expectorants, anti-coagulants, analgesics, antipyretics, antiemetics and/or bronchodilators; refer also to section 6.8 regarding permitted prior or concurrent therapy
- Treatments for COVID-19 which are: Administered in accordance with approved conditions by the national health authority (*Specific for India*; Indian Council for Medical Research (ICMR) guidelines for management of COVID-19 patients (ICMR, 2021)), including emergency use authorizations, conditional approvals, or article 5(3) reviews,

  AND

- Approved under such conditions in the US or EU, and/or recommended in international consensus guidelines (e.g., remdesivir, dexamethasone, tocilizumab, convalescent plasma, and certain monoclonal antibodies). See section 6.8 regarding permitted prior or concurrent therapy.

10.5. Appendix 5: Country-specific Requirements

10.5.1. India

The trial will be a phase 2/3 trial. 80 subjects will be enrolled from India in the phase 2 part of the trial.

Protocol title: A randomized, double-blind, placebo-controlled, parallel group, phase 2/3, multicenter trial investigating the efficacy and safety of C21 as add on to standard of care in adult subjects with COVID-19.

Inclusion criterion 1: Age ≥18 at the time of signing the informed consent, to ≤65 years.

Inclusion criterion 7: *Specific for India*: For subjects with an ordinal scale score of 5, moderate to severe COVID-19 disease confirmed by at an $SpO_2 \leq 93$ % or a respiratory rate ≥ 24/min on room air. Note: If a subject is on supplemental oxygen with SpO2 >93% and respiratory rate <24/min, but desaturation to ≤ 93 % or increase of respiratory rate to ≥ 24/min on lower supplemental oxygen or room air is documented during screening, the inclusion criterion is considered to be met.

Standard of Care for COVID-19 includes the ICMR guidelines for management of COVID-19 patients (ICMR, 2021) (ICMR, 2021).

10.6. Appendix 6: Abbreviations

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
ANCOVA	Analysis of covariance
ALT	Alanine Transferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AT1R	Angiotensin II type 1 Receptor
AT2R	Angiotensin II type 2 Receptor
BCRP	Breast Cancer Resistance Protein
b.i.d.	bis in die (i.e. twice a day)
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulation
COVID-19	Corona Virus Disease 2019
CYP	Cytochrome P450
CYP1A2	Cytochrome P450 Family 1 Subfamily A Member 2
CYP2C9	Cytochrome P450 Family 2 Subfamily C Member 9
CYP3A4	Cytochrome P450 Family 3 Subfamily A Member 4
DMC	Data Monitoring Committee
ECMO	Extra Corporeal Membrane Oxygenation
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
EWD	Early Withdrawal
FiO_2	Fraction of inspired Oxygen
GCP	Good Clinical Practice

HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICMR	Indian Council for Medical Research
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IMP	Investigational Medicinal Product
LDH	Lactate Dehydrogenase
MCV	Mean Corpuscular Volume
MDR1	Multi Drug Resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase Chain Reaction
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Retrograde P waves
QTc	QT corrected
QTcF	QT corrected by Fridericia
QTL	Quality Tolerance Limits
RAS	Renin Angiotensin System
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SpO_2	Peripheral Capillary Oxygen Saturation
SoA	Schedule of Activities
SoC	Standard of Care

WOCBP	Woman of Childbearing Potential
WONCBP	Woman of non-childbearing Potential

11. Protocol Amendment History

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Description of Change**	**Rationale for changes**
Final protocol, version 1.0, dated 14-Apr-2021	First version	
Amendment 1 to the protocol. Non-substantial. Final protocol, version 2.0, dated 06-May-2021.	Section 2.2. Background Statistical conclusion on the primary endpoint in the phase 2 trial added. Section 5.2 Exclusion Criteria Exclusion criterion: Impaired hepatic function (i.e., Child-Pugh class A or B) changed to Impaired hepatic function (i.e., Child-Pugh class B or C). Section 9.3.3 Secondary Endpoint Analysis Removal of text describing the change from baseline ordinal scale score analysis.	Sentence added to provide more clarity. Correction of error in the exclusion criterion. Correction of error in the protocol.
Amendment 2 to the protocol. Substantial. Final protocol, version 3.0, dated 02-Jul-2021.	Section 1.1. Synopsis Endpoint, change in LDH added. Interim analysis and DMC process clarified. *Ad hoc* safety review meeting added. Section 3 Objectives, Endpoints, and Estimands	Endpoint added to include a lung injury biomarker. Per. authority request. and alignment with interim analysis plan. Endpoint added to include a lung injury biomarker.

	Endpoint, change in LDH added.	
	Section 4.2. Scientific rationale for Trial Design Description of individual change in ordinal scale scores reflected in the primary endpoint added.	Additional clarification of the primary endpoint.
	Section 5.1 Inclusion Criteria Indian specific; Age limits and SpO_2 criteria added to inclusion criteria 1 and 7, respectively.	Per. authority request.
	Section 5.2 Exclusion Criteria	
	Active tuberculosis added to exclusion criterion 2.	Per. authority request.
	SpO2 / FiO2 ratio added to exclusion criterion 9.	Added if a blood gas test is not available.
	Section 6.2 Preparation, Handling, Storage and Accountability Oral dispersion and nasoenteral feeding tube added as alternative administration forms.	To align with common drug administration practices at hospitals treating COVID-19 patients.
	Section 6.8 Prior and Concomitant Therapy List with Prohibited medication added.	Per. authority request.

	Section 7.1 Discontinuation of Investigational Medicinal Product IMP discontinuation criteria added for acute kidney and hepatic injury.	Per. authority request.
	Section 7.1.1. Temporary discontinuation Text updated to specify that there are no specific criteria for temporary discontinuation of IMP in the protocol.	Wording updated for clarification.
	Section 8.2.1 8-point ordinal Scale Additional 8-point ordinal scale assessment added at time of hospital discharge and in patients hospitalized between Day 29 and 60.	Improve data collection.
	8.3 Survival and Hospitalization Section updated to collect data on all types of hospital re-admissions.	Per. authority request.
	8.4.4. Clinical Safety Laboratory Tests Albumin and LDH added to lab parameters.	Albumin added to assess hepatic impairment using the Child-Pugh system. LDH added as a biomarker for lung injury.
	8.4.5 Hepatic Impairment Serum albumin added to Child-Pugh System table.	Correction of error in the protocol.

	9.3.3. Secondary Endpoint Analysis Added that the cumulative distribution functions will be plotted for the oxygen supplemental free days up to Day 29 endpoint.	To aid the interpretation of the results.
	Plots of cumulative distribution functions added.	Per. authority request.
	9.3.4 Exploratory Endpoint Analysis LDH added.	LDH added as laboratory assessment.
	9.3.6 Other analysis Added text on additional sensitivity analyses.	Per. authority request.
	9.4 Interim Analysis Additional details on the interim analysis provided including a cap of 450 subjects per. treatment arm.	Additional clarifications on the interim analysis.
	10.1.5.1. Data monitoring committee Option for a third DMC meeting added.	Per authority request.
	10.3 Appendix 3: Contraceptive and Barrier Guidance Abstinence removed.	Per authority request.
	10.3.2 Definitions Procedure for discontinuation of HRT to check menopausal status removed.	Per authority request.

	10.4 Appendix 4 Standard of Care for COVID-19 Section added. Section 10.5 Appendix 5: Country-specific Requirements for India added.	Per authority request. Per authority request.
Amendment 3 to the protocol. Substantial. Final protocol, Version 4.0, dated 07-Dec-2021.	Added section including contact details for 24/7 medical coverage Section 1.3 Schedule of Activities Section 5.1 Inclusion criteria Added "hospital-approved diagnostic" PCR test to inclusion criterion 2. Section 5.2 Exclusion criteria Exclusion criterion 3 rephrased to clarify that the alterations in the Child-Pugh score are caused by altered hepatic function, not another underlying disease. Section 5.2 Exclusion criteria Exclusion criterion 5 changed to a COVID-19 symptom onset >21 days prior to screening (Visit 1).	In accordance with the information already distributed to the sites. Added possibility to use local lab for analysis of safety samples in special circumstances. Per authority request. Clarification of the severity assessment of hepatic impairment. To align with new evidence suggesting that subjects infected with SARS-CoV-2 after vaccination have a longer duration of illness (Antonelli et al., 2021).

	Section 6.2 Preparation, Handling, Storage and Accountability Oral dispersion added as option for patients with gastric discomfort Specified that route of administration is captured in eCRF.	To align with common practice at hospital treating patients with gastric discomfort. Data collection further specified.
	Section 7.1 Discontinuation of Investigational Medical Product Clarify the assessment of severity of hepatic impairment.	Clarification and alignment with Exclusion criterion 3.
	Section 8.4.4. Clinical Safety Laboratory Tests Added option of local laboratory analysis of safety samples in special circumstances	To ensure subjects safety and sufficient medical oversight of enrolled subjects e.g. in case of prolonged turnaround time for analysis of lab samples at central lab.
	Section 8.4.5 Hepatic Impairment Clarification of grading of Hepatic Impairment Update of Table 3	To ensure that impaired hepatic function, not another underlying disease, is the cause of alterations in the Child Pugh components. To include central lab units to ease the process for sites.
	Section 9.3.5 Safety analysis Clarify the type of shift tables to be produced.	Alignment with SAP.
	Section 9.3.6 Other analyses. Sub-group analysis including presence of risk factors for severe COVID-19 added	Alignment with SAP.

	Section 9.4 Interim analysis Clarified that no adjustment for alpha will be required.	Per authority request.
Amendment 4 to protocol. Substantial. Final protocol, Version 5.0, dated 13-Apr-2022.	Overall changes (all changes were implemented without access to unblinded data from the ongoing trial): The primary endpoint has been changed from *proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15* to *all-cause mortality up to Day 60*. The previous primary endpoint is now considered a key secondary endpoint. Major changes throughout the document to reflect the new primary endpoint for the trial Sections 1.1, 3.0, 4.2, 9.1.1, 9.3.2 and 9.3.3 have been updated to reflect these changes.	Since trial planning, the assumptions for the primary endpoint have changed and the current primary endpoint is not likely to reflect the presumed benefit of C21. The new primary endpoint will ensure capturing the majority of clinical events to assess a treatment response and thus evaluate the complete treatment effect over time.

	Sample Size has been reduced from 600 to maximum 300 patients. Section 1.1, 1.2, 4.1, 9.3.1 and 9.5 have been updated to reflect the reduced sample size. Power calculations have been updated to incorporate the new primary endpoint.	Due to the current instable geopolitical situation and to ensure patient safety and data integrity in the trial, the Sponsor has closed all clinical sites in the Ukraine and Russia. This impacts enrolment, and a significant challenge in completing the recruitment is foreseen. Current estimates indicate that the target 600 patients will not be reached in a foreseeable future and is contingent on the occurrence of new COVID-19 waves with virus variants of a more severe phenotype. The Sponsor has decided to complete the trial when a maximum of 300 patients have been enrolled.
	Removal of Interim Analysis revised in section 9.4	Due to decreased sample size.
	Decrease of PK sample size revised in section 1.3 and 8.6	Due to decreased sample size.
	Section 9.2 Analysis sets	In alignment with SAP.
	Section 9.3.6 Other analyses Added race and ethnicity	Per Authority request.

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