CLINICAL STUDY PROTOCOL: ABC-201

Title:	Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2/3 Study, in Adult Subjects Hospitalized with Severe SARS-CoV-2 Positive Pneumonia
Name of Investigational Product:	Opaganib (ABC294640)
Phase of Development:	Adaptive Phase 2/3, with Futility Analysis
Protocol Identification:	ABC-201
Sponsor Name and Address:	RedHill Biopharma Ltd. 21 Ha'arba'a St. Tel-Aviv 6473921, Israel Tel: +972 (0)3 541 3131 Fax: +972 (0)3 541 3144
Compliance Statement:	The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable national and local regulations., including the Rules of Good Clinical Practice of the Eurasian Economic Union, the EU Commission, the European Medicines Agency (EMA), and the Heads of Medicines Agency (HMA). In addition, the study complies with Interim guidelines: Prevention, diagnostics and treatment of a new coronavirus infection (COVID-19), MOH of the Russian Federation and specific guidance to the Sponsor from the Italian Medicines Agency (AIFA). The study has also taken into account the FDA COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products Guidance for Industry and Investigators (May 2020) as well as the WHO Working R&D Blueprint for COVID-19: Informal consultation on the potential inclusion of Immunomodulators in a clinical trial 06 May 2020.

Date of Protocol Amendment:	Original: Version 1.0, 03 June 2020 Version 1.1, dated 15 June 2020
Name: Title: Phone:	Signature

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2 APPROVALS

Sponsor Representatives

06-15-2020

Reza Fathi, PhD Date
Senior Vice President, Research and Development
RedHill Biopharma Ltd.

16-June-2020

Mark L. Levitt MD PhD Date
Medical Monitor

3 PROTOCOL SYNOPSIS

Study Title	Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2/3 Study, in Adult Subjects Hospitalized with Severe SARS-CoV-2 Positive Pneumonia
Protocol Number	ABC-201
Sponsor	RedHill Biopharma Ltd.
Investigational Product	Opaganib (ABC294640)
Opaganib	Opaganib [3-(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl)amide, hydrochloride salt] is an orally available inhibitor of the enzyme sphingosine kinase-2 (SK2) (French, 2010). SK2 is an innovative molecular target due to its critical role in sphingolipid metabolism, which is known to regulate many cellular functions, including the replication-transcription complex (RTC) of +single-strand RNA viruses
Rationale-Preclinical	Opaganib is an investigational product in early clinical development with anti-viral properties targeting RNA viruses, such as coronaviruses, by inhibiting viral replication, combined with anti-inflammatory effects as detailed below. Opaganib has been studied in pre-clinical models of RNA viral disease, inflammation and cancer (see Investigator Brochure). Inhibition of the enzyme sphingosine kinase-2 (SK2) with opaganib has demonstrated a decrease in viral titers of influenza virus in an in vitro model system (with an EC50 well within the achievable concentrations of opaganib in humans, based on the phase 1 human trial) as well as improved survival in a preclinical study of influenza infected mice receiving opaganib daily for two days. Opaganib has also demonstrated a substantial inhibitory effect in a dose dependent manner in a preliminary Ebola cell-based inhibition assay with near complete inhibition of Ebola cellular infection with the same achievable concentrations of opaganib in humans. Targeted knockdown of SK2 also inhibited Hepatitis C virus replication and substantially reduced Chikungunya Virus in infected HepG2 cells. The pre-clinical effect on Chikungunya Virus is particularly relevant as they also contain a +single stranded RNA genome like SARS-CoV-2 and other corona viruses. In

	chikungunya viral infection, SK2 has been shown to be recruited to the viral replication transcription complex by the viral Nsp3 protein, and its inhibition substantially reduces viral replication. Opaganib has also been shown to inhibit host inflammatory responses in vitro and in vivo by blocking the phosphorylation of sphingosine to sphingosine-1-phosphate (S1P), preventing the pro-inflammatory effects of S1P in a number of disease models as well as in a radioprotection model. Opaganib has shown a decrease in IL-6 levels, in TLR4 expression, NF-κB activation and TNFα-induced activation of NFκB pro-inflammatory cytokine/ chemokine (TNFα, IL-1β and CXCL-10) production; a decrease in monocyte/ macrophage and neutrophil tissue infiltration; blocking of CD4+ T cell infiltration and IFNγ production; abrogation of TNFα-induced expression of adhesion proteins and blockade of TNFα-induced PGE2 (as a measure of COX-2 activity). In an in vivo model of *Pseudomonas aeruginosa* pneumonia, opaganib has been shown to reduce TNF-alpha and IL-6 concentrations in bronchioloalveolar lavage fluid to near non-infected control levels. The decision to enroll patients into this study and, in some cases, add opaganib to other experimental medicines, will be at the discretion the study physician, based on the pharmacological action, existing data and dosage form described in this protocol. Of note, in patients who are unable to swallow capsules, opaganib made into a suspension form may be administered via a nasogastric tube (administering opaganib suspension via nasogastric tube did not substantially alter the bioavailability of opaganib after a tube fee in a healthy volunteer study).
Rationale-Clinical Studies to Date	To date, three clinical trials have been completed with opaganib, a phase 1 food and administration route effect study in healthy volunteers, a phase 1b study in advanced solid tumor patients, and a phase 1b/2 study in patients with advanced multiple myeloma. Two additional studies are currently in progress, a phase 2 study in patients with cholangiocarcinoma and a phase 2 study in patients with castration-resistant prostate cancer. In May 2020 the U.S. FDA approved a Phase 2a clinical study evaluating opaganib in patients with confirmed moderate-to-severe SARS-CoV-2 infection. Based on the Phase 1b studies, the dose of 500 mg of opaganib every 12 hours was determined as the maximum safe and tolerable dose in treatment in oncology patients. This same dose will be utilized in the COVID-19 studies.

	Of note, the dose and duration (exposure) proposed for COVID-19 patients is considerably shorter than that in oncology patients, who have received opaganib daily for up to 2 years.
Compassionate Use Experience in COVID-19 Infection	To date, 7 patients with severe COVID-19 infections have been treated with opaganib on compassionate exemption. These results are uncontrolled however provide important clinical data within the compassionate use context. One patient improved 36 hours after initiation of treatment to room air and was discharged from hospital. Five other patients were treated with opaganib for up to 14 days. All patients had clinical improvement and were discharged from hospital. Patients treated with opaganib in the compassionate use program did not progress to requiring intubation and mechanical ventilation. Patients receiving opaganib via compassionate use were compared to a matched case-control group of 18 patients. Opaganib treated patients had faster improvement in lymphocyte counts, decreased CRP and faster time to being weaned off high flow oxygen. Of the 18 match controls, 6/18 cases required intubation and mechanical ventilation. One patient started hydroxychloroquine, azithromycin and opaganib within 24 hours and had diarrhea necessitating withdrawal of all three medications. This was the only adverse event thought to be at least possibly related to opaganib.
Standard of Care Considerations	To date, only 2 medicinal therapies have received emergency use authorizations as standard of care world-wide. These are chloroquine/hydroxychloroquine/ mefloquine and remdesivir. As new data emerge for hydroxychloroquine for the risk-benefit in COVID-19, emergency use authorization has been withdrawn in some countries, therefore, as the approval and/or guidance for treating COVID-19 are evolving, for this protocol, standard of care will be defined by the recommended schemes of treatment according to the severity of the disease based on local diagnostic and guideline documents such as the Temporary Methodic Recommendations: Prophylactic, Diagnostics and Treatment of New Corona Virus Infection (COVID-19) (Appendix 10); the EU Commission, the European Medicines Agency (EMA), and the Heads of Medicines Agency (HMA), and as updated to the most current version of the recommendations. All other treatments will be considered experimental, pending evaluation and potential future approval. Concomitant use of standard of care, and/or experimental treatments in patients enrolled in this study will be guided by the

	inclusion/exclusion criteria, prohibited medications and precautionary medications as outlined in the protocol and the study physician's discretion.
Justification for Opaganib, Population, Study Design, Primary	The population to be enrolled in this study will have severe COVID-19 infection, be hospitalized and require supplemental oxygen to treat hypoxemia, with or without an increased work of breathing. The effect of opaganib, as an anti-viral and anti-inflammatory medicine, if effective, is likely to provide the most measurable benefit at this clinical stage of severity. As the primary objective of opaganib therapy is to improve and/or stabilize the clinical status of the patient, the primary analysis is based on the proportion of patients who deteriorate clinically and progress to require invasive ventilation (intubation and mechanical ventilation). This outcome will be considered a treatment failure. Patients who die prior to Day 14 will also be considered to have met treatment failure. The primary endpoint is consistent with the WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis and corresponds to achieving Score 6, 7 or 8 on the WHO Ordinal Scale for Clinical Improvement. The duration of treatment is 14 days, aligns with approved anti-viral treatment regimens for COVID-19, such as remdesivir.
Primary Objective	To evaluate the proportion of patients requiring intubation and mechanical ventilation by Day 14
Secondary Objectives	1) To evaluate change on the WHO Ordinal Scale for Clinical Improvement 2) To evaluate the time to intubation and mechanical ventilation 3) To evaluate the time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or CPAP, if high oxygen flow is not an available option 4) To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14 5) To evaluate the total oxygen requirement (area under the curve) using daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14) 6) To evaluate the time to two consecutive negative swabs for SARS-CoV-2 by PCR

	7) To evaluate the proportion of patients with two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14 8) To evaluate the proportion of patients, with at least one measurement of fever at baseline (defined as temperature >38.0 C [100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14 9) To evaluate mortality 30 days post-baseline
Exploratory Objectives	To assess the change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) over the treatment period of 14 days
Safety Objectives	To assess the safety and tolerability of opaganib administered orally at 500 mg Q 12 hours, for up to 14 days, in patients with severe COVID-19 pneumonia
Study Population	The study population will consist of patients diagnosed with COVID-19 infection that is defined as severe based on eligibility criteria to align with current region-specific diagnostic guidance. Specifically patients will at minimum have pneumonia secondary to SARS-CoV-2, radiographic evidence of pneumonia on chest X-ray or CT scan, and require supplemental oxygen by high flow oxygen via nasal cannula or CPAP, if high oxygen flow is not an available option. Patients must be hospitalized at least during screening and at Baseline (Day 1).
Study Design and Description	This is a phase 2/3 multi-center randomized, double-blind, parallel arm, placebo-controlled study with an adaptive design that will utilize a futility assessment. The study is planned be performed in Italy, other EU countries, Russia, Brazil, Mexico and the US in up to approximately 40 clinical sites. After informed consent is obtained, patients will enter a screening phase for no more than 3 days, to determine eligibility. Approximately 270 eligible patients will be randomized and receive either opaganib added to standard of care, or matching placebo added to standard of care, in a randomization ratio of 1:1. Treatment assignments will remain blinded to the patient, investigator and hospital staff, as well as the sponsor. As the approval and/or guidance for treating COVID-19 are evolving, for this protocol, standard of care will be defined by the recommended schemes of treatment according to the severity of the disease based on local diagnostic and guideline documents such as the Temporary Methodic Recommendations: Prophylactic, Diagnostics and Treatment of New Corona Virus Infection (COVID-19) (Appendix 10); the EU Commission, the European

	Medicines Agency (EMA), the Heads of Medicines Agency (HMA) and FDA, and as updated to the most current version of the recommendations. Study participants will receive either opaganib 2 x 250 mg capsules (500 mg) every 12 hours, or matching placebo, in addition to standard of care (pharmacological as defined above and/or supportive) at any given institution. Study drug will be administered every day for 14 days (Day 1 to Day 14). All participants will be followed up for 28 days after their last dose of study drug, which may occur at Day 14 or after premature study drug discontinuation, based upon patient or physician determination.
Randomization Strategy	As the treatments in the recommended schemes of treatment according to the severity of the disease may differ, based on local diagnostic and guideline documents such as the Temporary Methodic Recommendations: Prophylactic, Diagnostics and Treatment of New Corona Virus Infection (COVID-19) (Appendix 10); the EU Commission, the European Medicines Agency (EMA), the Heads of Medicines Agency (HMA) and the FDA, standard of care administered to patients may differ by institution. In order to ensure balance of standard treatment regimens in both treatment arms randomization will be determined at the individual site level
Adaptive Interim Analysis for Futility	An unblinded futility interim analysis will be conducted when approximately 100 subjects (approximately 50 subjects from each group) have been evaluated for the primary endpoint to determine the probability of rejecting the null hypothesis of no effect and if it would be futile to continue the study. Criteria will be prospectively determined and documented in the final version of the Statistical Analysis Plan (SAP) prior to the interim analysis.
Data Safety Monitoring Committee	A data safety monitoring board (DSMB) will be convened for the safety oversight of the study in order to assuring safety of the trial participants. The DSMB meetings to review the safety data, will be planned after 25%, 50% and 75% or when approximately 70, 135 and 200 randomized patients, respectively, have reached Day 7, and then Day 14. The DSMB will also be responsible for conveying the results of the futility analysis conducted by an independent unblinded statistician to the sponsor (futile/non-futile). A DSMB charter will be provided as a separate document.
Stratification	Patients will be stratified based on meeting three or more high risk clinical parameters for COVID-19 outcomes at baseline (yes or no)

	The parameters are: 1) age at screening, ≥60 years of age, (yes or no); 2) male, (yes or no); 3) HbA1c at screening, ≥6.5 (yes or no); 4) hypoxemia without commensurate increased work of breathing (defined as increased respiratory rate, nasal flaring and/or increase use of respiratory muscles including the diaphragm [yes or no]; 5) known underlying chronic lung disease (yes or no); 6) known cardiovascular disease or hypertension (yes or no); 7) BMI ≥ 28.0 kg/m^2 (yes or no); 8) known renal disease (yes or no).
Treatment and Administration	Opaganib 500 mg Q12 hour or matching placebo Opaganib or placebo made into a suspension form may be administered by nasogastric tube,
Study Duration	Recruitment period is estimated at 4 months The maximum duration of study participation will be up to 45 days (including up to 3 days screening; up to 14 days of double-blind treatment and 28 days off-study drug follow-up)
Eligibility Criteria	***Inclusion:*** 1. Adult male or female ≥18 to ≤80 years of age 2. Proven COVID-19 infection per RT-PCR assay of a pharyngeal sample (nasopharyngeal or oropharyngeal) AND pneumonia defined as radiographic opacities on chest X-ray or CT scan 3. The patient requires, at baseline, high flow supplemental oxygen or CPAP, if high oxygen flow is not an available option. 4. Patient agrees to use appropriate methods of contraception during the study and 3 months after the last dose of study drug 5. The patient or legal representative has signed a written informed consent approved by the IRB/Ethics Committee ***Exclusion:*** 1. Any co-morbidity that may add risk to the treatment in the judgement of the investigator. 2. Requiring intubation and mechanical ventilation

	3. Oxygen saturation ≥95% on room air 4. Any preexisting respiratory condition that requires intermittent or continuous ambulatory oxygen prior to hospitalization 5. Patient is, in the investigator's clinical judgement, unlikely to survive >72 hours 6. Pregnant (positive serum or urine test within 3 days prior to randomization) or nursing women . 7. Unwillingness or inability to comply with procedures required in this protocol. 8. Corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms for females or >450 ms for males, calculated using Friedericia's formula (QTcF) 9. AST (SGOT) or ALT (SGPT) > 2.5 x upper limit of normal (ULN) 10. Total bilirubin >1.5x ULN (except where bilirubin increase is due to Gilbert's Syndrome) 11. Serum creatinine >2.0 X ULN 12. Absolute neutrophil count <1000 cells/mm^3 13. Platelet count <75,000/mm^3 14. Hemoglobin <8.0 g/dL 15. Currently taking medications that are sensitive CYP3A4, CYP2C9 or CYP2C19 substrates and have a narrow therapeutic index 16. Currently taking medications that are strong inducers or inhibitors of CYP2D6 and CYP3A4 17. Currently taking warfarin, apixaban, argatroban or rivaroxaban due to drug-drug interaction based on CYP450 metabolism 18. Current drug or alcohol abuse 19. Currently participating in a clinical study assessing pharmacological treatments, including anti-viral studies
Number of Subjects	Approximately up to 300 subjects will be screened to randomize approximately 270 subjects

Number of Investigator Sites	Up to approximately 40 participating hospital centers
Screening/Baseline Assessments	• Signed informed consent by patient or legal representative • Eligibility determination • Complete medical history (including onset of COVID-19 symptoms) • Concomitant medication assessment • Baseline review of systems • Physical examination • Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter) • Weight if the patient is ambulatory • Oxygen requirement (L/min) • FiO2 (estimate) • 12-lead electrocardiogram • Chest Xray or CT scan • Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 PCR test • Serum chemistry • CRP, D-Dimer, LDH, ferritin, cardiac troponin • HbA1c • CBC with differential • Urinalysis • Serum or urine pregnancy test (for women of childbearing potential) within 3 days prior to treatment

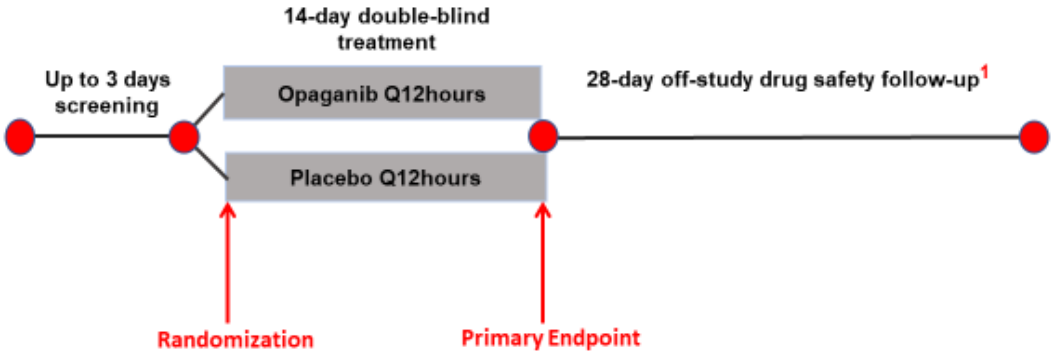
Study Assessments	The following will be monitored and documented daily as part of the standard of care: • Concomitant medications • Adverse Events • Interim Physical exam • Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter) • Oxygen flow rate setting (L/min) • FiO2 (estimate or known if patient is ventilated) The following will be monitored less frequently as part of standard of care and wherever possible: • For patients on concomitant chloroquine/hydroxychloroquine/mefloquine, a 12-lead electrocardiogram (if allowed by hospital treatment guidelines under COVID-19) approximately 3 hours after the first study drug administration on Day 1, anytime on Days 2 and 4, and again at end-of-treatment (either Day 14 or at premature study drug discontinuation). If patients are on monitors (including telemetry or Holter monitors), investigators are encouraged to collect QT interval data • Nasopharyngeal or oropharyngeal viral swab for SARS-CoV-2 PCR test every 3 days • Serum chemistry once weekly • Serum CRP, D-Dimer, LDH, ferritin, cardiac troponin once weekly • CBC with differential once weekly • Chest X-ray or CT scan as per physician decision
Study Endpoints	**Primary** The percentage of patients requiring intubation and mechanical ventilation by Day 14 **Secondary**

	1) The percentage of patients with ≥2 category improvement on the WHO Ordinal Scale for Clinical Improvement 2) The time to intubation and mechanical ventilation 3) The time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or CPAP, if high oxygen flow is not an available option 4) The percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14 5) The total oxygen requirement (area under the curve) using the daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14) 6) The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart 7) The percentage of patients with at least two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14 8) The percentage of patients with at least one measurement of fever at baseline (defined as temperature >38.0 C[100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14 9) Mortality due to any cause at Day 30 after baseline **Exploratory** The mean change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], procalcitonin [PCT], lactate dehydrogenase [LDH] and ferritin) from baseline at Day 14 **Safety** 1) Incidence rates of all treatment-emergent AEs (TEAEs) and SAEs 2) Evaluation of vital signs 3) Evaluation of laboratory parameters (chemistry and hematology) 4) Evaluation of electrocardiograms (ECG)
Prohibited Medications	The following medications are prohibited during the study, including the 28-day follow-up period:

during the Study	• Medications that are sensitive CYP3A4, CYP2C9 or CYP2C19 substrates and have a narrow therapeutic index are prohibited • Strong inducers or inhibitors of CYP2D6 and 3A4 are prohibited • Warfarin, apixaban, argatroban and rivaroxaban are prohibited due to drug-drug interaction based on CYP450 metabolism
Adverse Events of Special Interest	Opaganib may cause neuropsychiatric toxicity that may be due to increases in ceramides. In a Phase 1 healthy volunteer food effect study, these toxicities were found to be reduced by eating a light to moderate meal prior to each dose administration and this was likely due to delayed absorption and reduced Cmax. Neuropsychiatric events reported in clinical studies to date include: hallucinations, anxiety, insomnia, lethargy, agitation, distress and dysarthria. These neuropsychiatric adverse events occurred at higher frequencies at the highest dose administered, which is above the dose selected (best tolerated dose) for the current and future clinical studies.
Stopping Rules	At any time during the study, participants will stop study drug if it is determined that they have experienced any of the following adverse events (using Grading criteria as defined in the revised NCI Common Terminology for Adverse Events [CTCAE v.5.0]) • Any neuropsychiatric adverse event of Grade 3 severity • Hallucinations of any severity (any Grade) • Nausea of Grade 3 severity • Vomiting of Grade 3 severity • Creatinine increase of Grade 2 severity
Sample Size Estimation	It is planned to enroll approximately 270 eligible patients into the double-blind treatment phase, to receive either opaganib added to standard of care (n=135), or matching placebo added to standard of care (n=135). The sample size calculation was based on powering the study with respect to the primary efficacy endpoint of proportions of patients requiring intubation and mechanical ventilation at 14 days. It was assumed that the mechanical ventilation rate at 14 days in the control arm would be 25% and that opaganib is expected to provide absolute 15% reduction of this rate, to a mechanical ventilation rate of 10%. A total of 270 subjects

	provides 90% power to detect the assumed difference in mechanical ventilation rate, using chi square test, at a two-sided α=0.05 level of significance.
Statistical Methods	The primary analysis will be based on a composite failure (Yes/No) variable, indicating if a subject had required intubation and mechanical ventilation or had died by study Day 14. In the rare case of unknown patient outcome (patient lost to follow up), it will also be counted as treatment failure for the primary analysis. If a patient initiates new investigational therapy for COVID-19 within 14 days, this will also be regarded, in the primary analysis, as treatment failure. The number and percentages of subjects with failure event will be tabulated per treatment group. A 95% confidence interval will be constructed for each proportion. A Cochran Mantel-Haenzel (CMH) test will compare the proportion of failure between the two groups, using the study stratification factors used for randomization, and corresponding risk difference estimate will be presented with 95% confidence interval. Exact confidence intervals will be used as needed. The significance level for this test will be two-sided 5%. In the case of small number of events (less than 5 events in any study arm), the Fisher exact test will be used. The number and percent of each of the failure types (intubation and mechanical ventilation) will be described by group. The primary analysis will be based on the modified Intent to treat population (mITT), which consist of all patients that were randomized and treated with at least one dose of study drug.

4 STUDY SCHEMATIC



[1] Off-study drug follow-up starts when study drug is stopped per protocol or after discontinuation per patient or physician decision

5 SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Assessments	*Screening*	*Treatment Phase*			*Early termination*	*Safety follow-up[10]*
	Days -3 - 1	*Day 1 Randomization*	*Day 7*	*Day 14[1]*		
ICF signed	X					
Inclusion/exclusion criteria	X					
Demographics; medical and surgical history	X					
Review concomitant medication(s)[2]	X	X	X	X	X	X
Review of adverse events[2]		X	X	X	X	X
Physical examination[2]	X		X	X	X	X
WHO questionnaire[3]	X	X	X	X		
Vital signs[2]	X	X	X	X	X	X
Oxygen flow (L/min)[2]	X	X	X	X	X	X
Weight[4]	X					
HbA1c	X					
Pharyngeal viral sample[5]	X	X	X	X	X	X
12-lead ECG[6]	X			X		
Chest X-ray or CT scan[7]	X					
Serum chemistry[7]	X		X	X		
Hematology (CBC with differential)[7]	X		X	X		
D-dimer, cardiac troponin, CRP, LDH, ferritin[8]	X		X	X		
Urinalysis	X					

Assessments	*Screening*	*Treatment Phase*			*Early termination*	*Safety follow-up[10]*
	Days -3 - 1	*Day 1 Randomization*	*Day 7*	*Day 14[1]*		
Serum or urine pregnancy test[9]	X					

[1] Protocol defined End of Treatment (EOT) occurs on Day 14
[2]daily assessments whilst patient is hospitalized; vital signs = temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter and recording of supplemental oxygen requirement as oxygen flow (L/min)
[3] For WHO questionnaire (WHO ordinal scale for clinical improvement) -refer to Appendix 1
[4]record weight if patient is ambulatory
[5] pharyngeal samples for SARS-CoV-2 PCR are collected every 3 days, per standard of care. For patients having nasopharyngeal swabs, the same nostril must be used during the study
[/6] for patients on concomitant chloroquine/hydroxychloroquine/mefloquine, the 12-lead ECG will be repeated after 3 hours (±30mins) of initial dose, on Day 2 and Day 4
[7] Chest X-ray or CT scan, lab draws will be at the discretion of the Investigator depending on patient clinical condition
[8] CRP=C-reactive protein, LDH=lactate dehydrogenase
[9] women of childbearing potential; serum or urine pregnancy test must be negative within 3 days prior to randomization
[10] The follow-up visit may be performed by telephone if returning to the hospital site is not feasible per Investigator and/or patient decision. Only AEs, concomitant medications and oxygen flow will be collected by telephone.

6 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvate transaminase)
ARDS	Adult Respiratory Distress Syndrome
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
COVID-19	Coronavirus Disease of 2019
CFR	Code of Federal Regulations
CRO	Clinical Research Organization
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	United States Food and Drug Administration
FiO2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	NCI Common Terminology Criteria for Adverse Events
NG	Nasogastric
PCR	Polymerase Chain Reaction
QTc	Corrected QT
QTcF	Corrected QT using Friedericia's formula
RTC	Replication transcription complex
S1P	Sphingosine-1-phosphate
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan

SAE	Serious adverse event
SK2	Sphingosine kinase 2
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of the normal range
WHO	World Health Organization

7 BACKGROUND INFORMATION

7.1 COVID-19 Disease

COVID-19 is a newly recognized disease caused by a coronavirus virus, SARS-CoV-2. A flu-like illness was first noted in December 2019, in Wuhan, China and was subsequently attributed to a virus similar to the SARS coronavirus, which is now designated as SARS-CoV-2. While the clinical spectrum has not yet been well defined, early reports suggest that SAR-CoV-2 infection ranges from asymptomatic infection to pneumonia and Adult Respiratory Distress Syndrome (ARDS) with multiorgan failure, that may lead to death (Zhou, 2020). In the Zhou study, the median duration of viral shedding was 20 days, with an interquartile range of 17-24 days and a maximum of 37 days. Common symptoms reported in the Zhou study for 191 patients were fever (94%), cough (79%), sputum production and fatigue (each 23%) and myalgia (15%). Bilateral pulmonary infiltrates were noted in 75% of patients on chest X-ray. Patients over 65 years and those with significant comorbidities, such as diabetes, cardiac or pulmonary disease, appeared to be more susceptible for developing severe infection and had a relatively higher mortality rate compared to younger, otherwise healthy patients.

The incidence of symptomatic and severe infection, as a proportion of infected patients, is not yet known, as test availability, utilizing Polymerase Chan Reaction (PCR) performed on nasopharyngeal swabs or other body fluids, has been limited.

For most individuals testing positive, COVID-19 currently appears to be self-limiting. The major threat to this viral pandemic is spread through a nonimmune population, and to those most at risk of severe infection. SAR-CoV-2 is highly contagious, with spread by aerosol and surface contact (van Doremalen, 2020) and potential fecal spread (Chen, 2020). As this is a newly identified disease, first noted in December 2019, and as testing and interpretation of data are in a very early stage, no specific therapy has demonstrated antiviral efficacy.

7.2 Investigational Product

Opaganib [3-(4-chlorophenyl)-adamantane-1-carboxylic acid (pyridin-4-ylmethyl)amide, hydrochloride salt] is an orally available inhibitor of the enzyme sphingosine kinase-2 (SK2) (French, 2010). SK2 is an innovative molecular target due to its critical role in sphingolipid metabolism, which is known to regulate many cellular functions, including the replication-transcription complex (RTC) of +single-strand RNA viruses (Reid, 2015).

7.3 Preclinical Rationale

Preclinical studies demonstrate that opaganib both inhibits host inflammation and has anti-viral properties. Using $SK2^{-/-}$ mice and differential gene expression analysis, it was demonstrated that SK2/sphingosie-1-phosphate (S1P) signaling could play a key role in promoting pneumonia via

promoting inflammation and suppressing other factors that inhibit inflammation and host defense (Ebenezer, 2019). The results suggested that inhibition of SK2 may both inhibit viral replication and decrease pulmonary inflammation, ameliorating lung injury. Additional evidence for the anti-inflammatory properties of opaganib is derived from murine inflammatory bowl disease (IBD) models of ulcerative colitis, Crohn's disease and rodent models of inflammatory arthritis and liver ischemia reperfusion. Opaganib has been shown to suppress anti-inflammatory responses in-vitro and in-vivo, including:

1) decreased IL-6 levels, TLR4 expression, NF-κB activation and TNFα-induced activation of NFκB pro-inflammatory cytokine/ chemokine (TNFα, IL-1β and CXCL-10) production (Liu, 2010, Maines, 2008, Maines, 2010)
2) decreased infiltration of monocytes/ macrophages and neutrophils (Liu, 2012)
3) blocked CD4+ T cell infiltration and IFNγ production (Liu, 2012)
4) abrogation of TNFα-induced expression of adhesion proteins and blockade of TNFα-induced PGE2 as a measure of COX-2 activity (Maines, 2008).

Several other studies have reported that SK2 regulates cellular gene expression during Chikungunya virus (CHIKV) infection (Reid, 2015) and can maintain viral latency for Kaposi's sarcoma-associated herpesvirus (Dai, 2014). SK2 recruitment into the RTC has been demonstrated in CHIKV in the Togaviridae family of viruses which contains a non-segmented +single stranded RNA genome (COVID-19 is a +single stranded RNA genome). Treatment of infected HepG2 cells with opaganib significantly reduced CHIKV infection (Reid, 2015). Targeted knockdown of SK2 also inhibited hepatitis c virus (HCV) replication (Yamane, 2014).

Inhibition of SK2 with opaganib has also demonstrated a decrease in viral titers of influenza virus in an in vitro model system (with an EC50 well within the achievable concentrations of opaganib in humans, based on the phase 1 human trial) as well as improved survival in a preclinical study of influenza infected mice receiving opaganib daily for two days (Xia, 2018).

Opaganib has also demonstrated a substantial inhibitory effect in a dose dependent manner in a preliminary Ebola cell-based inhibition assay (RedHill Biopharma, unpublished data). The doses that displayed near complete inhibition of Ebola cellular infection are also achievable in humans.

7.4 Prior Clinical Experience

To date, three clinical trials have been completed with opaganib, a phase 1 food and administration route effect study in healthy volunteers, a phase 1b study in advanced solid tumor patients, and a phase 1b/2 study in patients with advanced multiple myeloma. . Two additional studies are currently in progress, a phase 2 study in patients with cholangiocarcinoma and a phase 2 study in patients with castration-resistant prostate cancer. Based on the Phase 1b studies, described in Section 7.4.1.1 and Section 7.4.1.2, based on safety and tolerability, the dose of 500 mg of opaganib every 12 hours was selected for future studies. The duration of treatment in oncology patients has been considerably

longer than that proposed for COVID-19 patients, with oncology patients receiving opaganib daily for up to 2 years.

In May 2020 the U.S. FDA approved a Phase 2a clinical study evaluating opaganib in patients with confirmed moderate-to-severe SARS-CoV-2 infection.

7.4.1 Completed Studies

7.4.1.1 Phase 1b Study in patients with advanced solid tumors (Study No. ABC-101)

Twenty-two patients were enrolled, of whom 21 were treated with doses from 250 mg QD through 750 mg BID. All 21 patients were evaluable for pharmacokinetics, pharmacodynamics and safety. Sixteen were evaluable for efficacy per RECIST 1.1 criteria. Patients received treatment continuously in 28 day cycles and treatment was given while fasting. Mean age of patients entered was 58 years. Seventy one percent were male, 67% white. All patients had received prior chemotherapy and approximately half had prior surgery and/or radiotherapy. Patients had a variety of concomitant medical conditions and were receiving a variety of medications in addition to their antitumor therapy.

The administered oral dose of 500 mg Q12 hours was the maximum tolerated dose. There were no deaths reported during the administration of opaganib. There were no discontinuations due to adverse events (AEs), in 250 mg QD and 250 mg bid cohorts. Common adverse events were nausea (12 patients, 57%), fatigue (12 patients, 57%), vomiting (8 patients, 38%) and neuropsychiatric effects (14 patients, 67%) including anxiety, insomnia, agitation and dysarthria. Of these, only fatigue appeared to be dose-related. Nausea and vomiting were common but not dose-limiting and rarely required discontinuation of treatment. Neuropsychiatric effects were seen at all dose levels, though were more common and bothersome at the highest dose level, 750 mg Q12 hours, considered an intolerable dose.

There were no consistent trends toward increases or grade shifts in liver function tests, hematologic parameters, or other biochemical parameters except for creatinine and lymphocytes. No patient developed clinically significant ECG abnormalities on study. There were no treatment group differences noted for the changes from baseline of QTcF. For more detailed data refer to Investigator Brochure.

7.4.1.2 Phase 1b Study in patients with advanced multiple myeloma (Study No. ABC-103

Thirteen patients received study drug: 3 at 250 mg Q12 hours, 4 at 500 mg Q12 hours and 6 at 750 mg Q12 hours. Median age of patients was 69 years (range 57-89), 7 were males, 7 were white and 6 black. All patients had received multiple courses of therapy with a median of 7 prior lines of treatment (range 3-13) excluding stem cell transplantation. Eight patients had autologous hematopoietic stem cell transplantation.

The administered oral dose of 500 mg Q12 hours was the maximum tolerated dose. There were no deaths reported during the administration of opaganib. Common adverse events included dyspepsia, nausea and vomiting. Eight patients experienced neuropsychiatric effects including altered mental state, confusion, dizziness, hallucinations and insomnia. All patients experiencing neuropsychiatric effects were receiving concomitant narcotic analgesics and several patients were also receiving other psychotropic medications. In several patients, after adjustment of the narcotic analgesic dosing regimen, the symptoms subsided, with maintenance or improvement of pain control. For more detailed data refer to Investigator Brochure.

7.4.1.3 Phase 1a Study of food and administration route effect study in healthy volunteers (Study No, ABC-109)

A total of 23 subjects participated in the study, 19 each received the drug orally in the fed and fasted states, and 21 via nasogastric (NG) tube. Mean and median ages of the subjects were 48.2 and 50.0 years, respectively (range 22-72 years). Of the subjects, 56.5% were males, 78.3% were white, and 47.8% were Hispanic. Median weight was 75.2 kg (range 52.0-123.3).

Subjects received a single 500 mg dose of opaganib (two 250 mg capsules) after a large standard meal, while fasting, and via nasogastric tube. Overall, 13 subjects (56.5%) experienced at least one treatment-emergent event (TEAE). Of these, 9/13 and 4/13 expereienced a Grade 1 and Grade 2 TEAE, respectively.

Overall, the most common TEAEs were nausea (3 subjects, 13%), diarrhea (3 subjects, 13%), dizziness (5 subjects, 21.7%) and headache (5 subjects, 21.7%). The drug was better tolerated after food as compared to the fasting state, with double the proportion of subjects experiencing TEAEs after fasted administration of opaganib compared to the fed state.

Administration with a large standard meal (fed state) resulted in prolongation of absorption, with an increase in time to maximum concentration by one hour and a 43% decrease in peak plasma concentration. Overall bioavailability (AUC0-inf) was reduced by 17% compared to fasted state. The change in bioavailability did not appear to affect pharmacologic activity, as S1P suppression, a pharmacologic consequence of SK2 inhibition, was somewhat higher after administration of opaganib in the fed state.

Administration of an opaganib suspension by nasogastric tube after tube feeding did not substantially alter bioavailability of the drug. Hence, subjects/patients who are unable to swallow capsules may take the drug in suspension form and via NG tube. For more detailed data refer to Investigator Brochure.

7.4.1.4 Compassionate Use Experience

To date, 7 patients with severe COVID-19 infections have been treated with opaganib on compassionate exemption. These results are uncontrolled however provide important clinical data within the compassionate use context. One patient improved 36 hours after initiation of treatment to

room air and was discharged from hospital. Five other patients were treated with opaganib for up to 14 days. All patients had clinical improvement and were discharged from hospital. Patients treated with opaganib in the compassionate use program did not progress to requiring intubation and mechanical ventilation.

Patients receiving opaganib via compassionate use were compared to a matched case-control group of 18 patients. Opaganib treated patients had faster improvement in lymphocyte counts, decreased CRP and faster time to being weaned off high flow oxygen. Of the 18 match controls, 6/18 cases required intubation and mechanical ventilation.

One patient started hydroxychloroquine, azithromycin and opaganib within 24 hours and had diarrhea necessitating withdrawal of all three medications. This was the only adverse event thought to be at least possibly related to opaganib.

8 RATIONALE FOR OPAGANIB IN COVID-19

Opaganib has demonstrated substantial anti-viral effects for RNA viruses in pre-clinical models. The novel SARS-CoV-2 virus, that has led to the recent global pandemic health crisis, is also an RNA virus for which opaganib has the potential to inhibit viral replication.

However, like all other experimental treatments at this time, opaganib has not been proven to be better or worse than the currently approved COVID-19 medicines. In this regard, its place among the existing experimental medicines will be at the discretion the study physician, based on the pharmacological action described above, existing data and dosage form. Of note, in patients who are unable to swallow capsules, opaganib made into a suspension form (refer to Section 12.6) may be administered via a nasogastric tube (administering opaganib suspension via nasogastric tube did not substantially alter the bioavailability of opaganib after a tube fee in a healthy volunteer study).

The population to be enrolled in this study will have severe COVID-19 infection, be hospitalized and require supplemental oxygen to treat hypoxemia, with or without an increased work of breathing. The effect of opaganib, as an anti-viral and anti-inflammatory medicine, if effective, is likely to provide the most measurable benefit at this clinical stage of severity.

9 STUDY OBJECTIVES

9.1 Primary

To evaluate the proportion of patients requiring intubation and mechanical ventilation by Day 14

9.2 Secondary

1) To evaluate change on the WHO Ordinal Scale for Clinical Improvement
2) To evaluate the time to intubation and mechanical ventilation
3) To evaluate the time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or CPAP, if high oxygen flow is not an available option
4) To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14
5) To evaluate the total oxygen requirement (area under the curve) using daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14)
6) To evaluate the time to two consecutive negative swabs for SARS-CoV-2 by PCR
7) To evaluate the proportion of patients with two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14
8) To evaluate the proportion of patients, with at least one measurement of fever at baseline (defined as temperature >38.0 C[100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14
9) To evaluate mortality 30 days post-baseline

9.3 Exploratory

To assess the change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) over the treatment period of 14 days

9.4 Safety

To assess the safety and tolerability of opaganib administered orally at 500 mg Q 12 hours, for up to 14 days, in patients with severe COVID-19 pneumonia.

10 STUDY POPULATION

The study population will consist of patients diagnosed with COVID-19 infection that is defined as severe based on eligibility criteria to align with current region-specific diagnostic guidance. Specifically, patients will at minimum have pneumonia secondary to SARS-CoV-2, radiographic evidence of pneumonia on chest X-ray or CT scan, and require supplemental oxygen by high flow oxygen via nasal cannula or CPAP, if high oxygen flow is not an available option. The patients must be hospitalized at least during screening and at baseline (Day 1).

11 ELIGIBILITY CRITERIA

11.1 Inclusion Criteria

1) Adult male or female ≥18 to ≤80 years of age
2) Proven COVID-19 infection per RT-PCR assay of a pharyngeal sample (nasopharyngeal or oropharyngeal) AND pneumonia defined as radiographic opacities on chest X-ray or CT scan
3) The patient requires, at baseline, high flow supplemental oxygen or CPAP, if high oxygen flow is not an available option
4) Patient agrees to use appropriate methods of contraception during the study and 3 months after the last dose of study drug
5) The patient or legal representative has signed a written informed consent approved by the IRB/Ethics Committee

11.2 Exclusion Criteria

1) Any co-morbidity that may add risk to the treatment in the judgement of the investigator.
2) Requiring intubation and mechanical ventilation
3) Oxygen saturation ≥95% on room air
4) Any preexisting respiratory condition that requires intermittent or continuous ambulatory oxygen prior to hospitalization
5) Patient is, in the investigator's clinical judgement, unlikely to survive >72 hours
6) Pregnant (positive serum or urine test within 3 days prior to randomization) or nursing women
7) Unwillingness or inability to comply with procedures required in this protocol.
8) Corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms for females or >450 ms for males, calculated using Friedericia's formula (QTcF)
9) AST (SGOT) or ALT (SGPT) > 2.5 x upper limit of normal (ULN)
10) Total bilirubin >1.5x ULN (except where bilirubin increase is due to Gilbert's Syndrome)
11) Serum creatinine >2.0 X ULN
12) Absolute neutrophil count <1000 cells/mm^3
13) Platelet count <75,000/mm^3

14) Hemoglobin <8.0 g/dL

15) Currently taking medications that are sensitive CYP3A4, CYP2C9 or CYP2C19 substrates and have a narrow therapeutic index

16) Currently taking medications that are strong inducers or inhibitors of CYP2D6 and CYP3A4

17) Currently taking warfarin, apixaban, argatroban or rivaroxaban due to drug-drug interaction based on CYP450 metabolism

18) Current drug or alcohol abuse

19) Currently participating in a clinical study assessing pharmacological treatments, including anti-viral studies

12 STUDY DESIGN

12.1 Overall Investigation Plan

This is a phase 2/3 multi-center randomized, double-blind, parallel arm, placebo-controlled study, with an adaptive design that will utilize a futility assessment. The study is planned to be performed in Italy, other EU countries, Russia, Brazil, Mexico and the US in up to approximately 40 clinical sites.

After informed consent is obtained, patients will enter a screening phase for no more than 3 days, to determine eligibility. Approximately 270 eligible patients will be randomized and receive either opaganib added to standard of care, or matching placebo added to standard of care, in a randomization ratio of 1:1. Treatment assignments will remain blinded to the patient, investigator and hospital staff, as well as the sponsor.

As the approval and/or guidance for treating COVID-19 are evolving, for this protocol, standard of care will be defined by the recommended schemes of treatment according to the severity of the disease based on local diagnostic and guideline documents such as the Temporary Methodic Recommendations: Prophylactic, Diagnostics and Treatment of New Corona Virus Infection (COVID-19) (Appendix 10); the EU Commission, the European Medicines Agency (EMA), the Heads of Medicines Agency (HMA) and FDA, and as updated to the most current version of the recommendations.

Study participants will receive either opaganib 2 x 250 mg capsules (500 mg) every 12 hours, or matching placebo, in addition to standard of care (pharmacological as defined above and/or supportive) at any given institution. Study drug will be administered every day for 14 days (Day 1 to Day 14).

All participants will be followed up for 28 days after their last dose of study drug, which may occur at Day 14 or after premature study drug discontinuation, based upon patient or physician determination.

The maximum duration of study participation will be up to 45 days (including up to 3 days screening; up to 14 days of double-blind treatment and 28 days off-study drug follow-up)

12.2 Randomization Strategy

As the treatments in the recommended schemes of treatment according to the severity of the disease may differ, as described in Section 12.1 above, standard of care administered to patients may differ by institution. In order to ensure balance of standard treatment regimens in both treatment arms randomization will be determined at the individual site level.

12.3 Study Assessments

The assessments for this study are listed in Section 14.1

12.4 Patient Discontinuation Criteria

A patient may be withdrawn from the study treatment or the study for any of the following reasons:

- Request of the patient or patient's representative
- AEs or adverse device effects (ADEs) based on the judgment of the Investigator
- The patient has experienced an AE that meets protocol defined stopping criteria (refer to Section 12.6.2)
- The Investigator decides that it is in the patient's best interest
- The patient is noncompliant with the protocol
- Lost to follow-up
- Death

If a subject is withdrawn at any time, the reason(s) will be recorded in the relevant section of the eCRF. Patients who discontinue from study treatment and remain in the study, will continued to be monitored per the Schedule of Assessments until Day 14 and the follow-up 28 days after stopping study drug.

Patients discontinued due to AEs or ADEs will be monitored until resolution or stability of the event based on the judgment of the investigator.

12.5 Study Drug Information and Dosage

12.5.1 Identification and Description of Investigational Drug

Opaganib 250 mg capsules contain the milled active opaganib drug substance along with the excipients microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate vegetal and are encapsulated in gelatin, white opaque body and cap, coni-snap capsules.

Opaganib will be supplied in bottles, each bottle containing 28 capsules

Placebo will be supplied in bottles, each bottle containing 28 capsules

Treatments will be blinded

12.5.2 Packaging and Labeling

The study medication will be packaged in bottles and labelled by the Sponsor.

The labels may include:

Protocol number

Subject number

Dispense Date

Name and contact information for the Sponsor

Route of administration: oral or nasogastric tube

Quantity supplied: 28 per bottle

Pharmaceutical dosage form: Capsules 250 mg

Storage conditions: store drug at 20-25°C (68-77°F) with excursions permitted to 30°C (86°F)

CAUTION: New Drug – Limited by Federal Law To Investigational Use

Bottle number

Lot number

12.5.3 Storage and Handling of Investigational Drug

Study drug should be stored at 20-25°C (68-77°F) with excursions permitted to 30°C (86°F).

12.6 Study Drug Administration

Study drug will be administered with food (after a light to moderate meal) and followed by 240 mL (8 fluid ounces) of water. If the patient can only take opaganib through a nasogastric tube, the contents of the capsule will be suspended in 20 cc normal saline solution and pushed through the nasogastric tube and flushed adequately with sterile water. If the patient is being tube-fed, study drug should be administered shortly after (approximately 15-30 minutes) a tube feeding.

12.6.1 Study Drug Dose Modification Plan for Study Drug Suspected Toxicities

Patients may undergo step-wise dose reduction to one capsule Q12 hours, as shown below. Patients who develop study drug related toxicity of ≥ Grade 2 at one capsule Q12 hours will not be permitted further dose reduction, and treatment will be discontinued. These patients will then enter a 28 day off-study drug safety follow-up period

NCI CTCAE 5.0 Criteria	**Study Drug Modification Instructions**
Any Grade 1 toxicity	For all Grade 1 toxicities, the Investigator may continue with study drug per the Investigator's discretion, without discussion with the sponsor
Any ≥ Grade 2 toxicity	The physician should discuss with the sponsor opaganib-related Grade 2 or greater toxicities that are likely to result in study drug discontinuation. A dose reduction may be considered as an alternative for continued treatment, after consultation with and approval by the sponsor. See criteria for stopping study drug in Section 12.6.2
Any ≥ Grade 2 neuropsychiatric toxicity	The physician should discuss with the sponsor opaganib-related Grade 2 or greater toxicities that are likely to result in study drug discontinuation. See criteria for stopping study drug in Section 12.6.2

12.6.2 Criteria for Stopping Study Drug

At any time during the study, participants will stop of study drug if it is determined that they have experienced any of the following adverse events (refer to section 17.2 Table 3 for Adverse Event Grade Definitions):

- Any neuropsychiatric adverse event of Grade 3 severity
- Hallucinations of any severity (any Grade)
- Lymphopenia of Grade 3 severity
- Nausea of Grade 3 severity

Dose Level	Dose (mg AM/PM)
1 (planned)	2 capsules/2 capsules
-1	1capsule/1 capsule

- Vomiting of Grade 3 severity
- Creatinine increase of Grade 2 severity

13 PRIOR AND CONCOMITANT MEDICATIONS

13.1.1 Prior Medications

Prior medications will include all recorded medications and supplements a patient was taking during the screening period that were stopped prior to administration of the study drug. These should be recorded in the eCRF.

13.1.2 Standard of Care Considerations

To date, only 2 medicinal therapies have received emergency use authorizations as standard of care world-wide. These are chloroquine/hydroxychloroquine/ mefloquine and remdesivir. As the approval and/or guidance for treating COVID-19 are evolving, for this protocol, standard of care will be defined by the recommended schemes of treatment according to the severity of the disease based on local diagnostic and guideline documents such as the Temporary Methodic Recommendations: Prophylactic, Diagnostics and Treatment of New Corona Virus Infection (COVID-19) (Appendix 10); the EU Commission, the European Medicines Agency (EMA), and the Heads of Medicines Agency (HMA), and as updated to the most current version of the recommendations.

All other treatments will be considered experimental, pending evaluation and potential future approval. Concomitant use of standard of care, and/or experimental treatments in patients enrolled in this study will be guided by the inclusion/exclusion criteria, prohibited medications and precautionary medications as outlined in the protocol and the study physician's discretion.

13.1.3 Allowed Medications

Necessary supportive measures for optimal medical care will be given throughout the study. Additional care may be administered as indicated by the treating physician and patient's medical need, and after discussion with the medical monitor.

13.1.4 Concomitant medications

Concomitant medications will include all medications that started, or were continuing, during or after administration of the study drug. All concomitant medications and supportive therapy administered starting Day 1 and until the final off-study drug follow-up visit must be recorded on the appropriate eCRF page.

13.1.5 Prohibited Medications

The following medications are prohibited during the study, including the 28-day follow-up period:

- Medications that are sensitive CYP3A4, CYP2C9 or CYP2C19 substrates and have a narrow therapeutic index are prohibited

- Strong inducers or inhibitors of CYP2D6 and 3A4 are prohibited
- Warfarin, apixaban, argatroban and rivaroxaban are prohibited due to drug-drug interaction based on CYP450 metabolism

14 SCHEDULE OF ASSESSMENTS

14.1 Procedures and Assessments

Please see "Schedule of Assessments" for a detailed study schedule (Section 5) presented in tabular form.

14.1.1 Screening (Day -3 to Day 1)

Prior to the initiation of study-specific screening assessments the Investigator or designee must provide the patient(s) a complete explanation of the purpose and evaluations (procedures and assessments) of the study. Subsequently, the patient, or legal representative, must sign and receive a copy of an Informed Consent Form and authorization of use and disclosure of protected health information (PHI) that was approved by the institutional review board (IRB). Once informed consent has been obtained, the eligibility of the patient will be determined, and Screening assessments will be performed. Screening may be performed prior to Baseline (Day -3 to -1) or on the same day as Baseline (Day 1)

- Signed informed consent
- Eligibility determination
- Complete medical history (including onset of COVID-19 symptoms)
- Concomitant medication assessment
- Baseline review of systems
- Physical examination
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter)
- Weight if the patient is ambulatory
- Oxygen requirement (L/min)
- FiO2 estimate
- 12-lead electrocardiogram
- Chest Xray or CT scan
- Nasopharyngeal or pharyngeal swab for SARS-CoV-2-PRC
- Serum chemistry
- CRP, D-Dimer, LDH, ferritin, cardiac troponin
- CBC with differential
- Urinalysis
- Serum or urine pregnancy test (for women of childbearing potential) within 3 days prior to treatment

14.1.2 The following will be monitored and documented daily as part of the standard of care

- Concomitant medications
- Adverse Events
- Interim Physical exam
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter)
- Oxygen requirement (L/min)
- FiO2 (estimate or known if patient is ventilated)

14.1.3 The following will be monitored less frequently as part of standard of care and wherever possible

- For patients on concomitant chloroquine/hydroxychloroquine/mefloqine, a 12-lead electrocardiogram (if allowed by hospital treatment guidelines under COVID-19) approximately 3 hours after the first study drug administration on Day 1, anytime on Days 2 and 4, and again at end-of-treatment (either Day 14 or at premature study drug discontinuation). If patients are on monitors (including telemetry or Holter monitors), investigators are encouraged to collect QT interval data
- Nasopharyngeal or oropharyngeal viral swab for SARS-CoV-2 PCR test every 1-3 days
- Serum chemistry once weekly
- Serum CRP, D-Dimer, LDH, ferritin, cardiac troponin once weekly
- CBS with differential once weekly
- Chest X-ray or CT scan as per physician decision

14.1.4 Safety Follow-up (28 days after last dose of study drug)

- Concomitant medications
- Adverse Events
- Physical exam
- Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter)
- Oxygen requirement (L/min)

The follow-up visit may be performed by telephone if returning to the hospital site is not feasible per Investigator and/or patient decision. Only AEs, concomitant medications and oxygen flow will be collected by telephone.

15 STUDY ENDPOINTS

15.1 Primary

The percentage of patients requiring intubation and mechanical ventilation by Day 14

15.2 Secondary

1) The percentage of patients with ≥2 category improvement on the WHO Ordinal Scale for Clinical Improvement
2) The time to intubation and mechanical ventilation
3) The time to low oxygen flow via nasal cannula e.g. from high oxygen flow via nasal cannula or CPAP, if high oxygen flow is not an available option
4) The percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14
5) The total oxygen requirement (area under the curve) using the daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14)
6) The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart
7) The percentage of patients with at least two consecutive negative swabs for SARS-CoV-2 by PCR at Day 14
8) The percentage of patients with at least one measurement of fever at baseline (defined as temperature >38.0 C[100.4 F]), who are afebrile (defined as temperature <37.2C [99 F]) at Day 14
9) Mortality due to any cause at Day 30 after baseline

15.3 Exploratory

The change in systemic markers of inflammation (D-dimer, cardiac troponin, C-reactive protein [CRP], lactate dehydrogenase [LDH] and ferritin) from baseline at Day 14

15.4 Safety

1) Incidence rates of all treatment-emergent AEs (TEAEs) and SAEs
2) Evaluation of vital signs
3) Evaluation of laboratory parameters (chemistry and hematology)
4) Evaluation of electrocardiograms (ECG)

16 SAFETY REPORTING

All adverse events should be reported to the sponsor on the provided data-capture forms. All serious adverse events should be reported within 24 hours of knowledge. If the serious adverse event results in a fatal or life threatening outcome, the sponsor and the medical monitor must be notified immediately.

Complete and fax or email a Serious Adverse Event report form and provide any supporting documentation to the Medical Monitor. The relevant forms to be completed as well as all contact details, including fax number and email addresses, will be provided in a separate document.

To discuss SAE with Medical Monitor, contact them directly by phone at the numbers provided in the separate document.

Follow-up information to a serious AEs must be provided to the Medical Monitor within 24 hours of investigator awareness in the same manner detailed above.

These serious adverse event reporting timelines must be followed in order for the sponsor to submit the safety information to the FDA within the safety reporting time regulations.

The medical monitor will notify all sites of any suspected, unexpected, serious adverse reactions (SUSARs). It is each Investigator’s responsibility to forward all SUSAR reports that are provided by the sponsor to their local IRB/EC. The sponsor will forward all SUSAR reports to central IRBs.

17 ADVERSE EVENTS DEFINITIONS

The following definitions of terms are guided by the United States Code of Federal Regulations (21 CFR 312.32(a)) and are included here.

An *Adverse Event (AE)* is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (may also be referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product and from any route of administration, formulation, or dose, including an overdose.

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose results in any of the following outcomes:

- death;
- is a life-threatening adverse event (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- requires in-patient hospitalization or causes prolongation of existing hospitalization;
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- is an important medical event. This is defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and be evaluated by the Sponsor for expedited reporting.

A *suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

A *Suspected Unexpected Serious Adverse Reaction* (SUSAR) is any (suspected) adverse reaction (any adverse event for which there is a reasonable possibility that the drug caused the adverse event) that is both serious and unexpected.

17.1 Assessment of Casual Relationship

The following categories and definitions for assessing the causal relationship of an event to the investigational product(s) are provided as a guide to be used for evaluating adverse events reported in this study to determine "suspected adverse reactions" that require expedited reported to regulatory agencies if they are unexpected. In addition to the assessment below, the aggregate number of occurrences will be considered to decide whether the event is a reportable event and requires an IND safety report.

Table 2. Relationship of Study Medication to Adverse Events

Unrelated	The study drug almost certainly (or certainly) did not cause the event. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another obvious etiology.
Probably not related	It is more likely that the event is due to another etiology than due to the study drug. Guidelines: There is no reasonable temporal relationship of the event to the administration of drug; The pattern is inconsistent with that known for the drug; and/or There is another more likely etiology.
Possibly related	It is approximately equally likely that the event is due to the study drug as it is due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The drug seems as likely as other etiologies to have caused the effect
Probably related	It is more likely that the event is due to the study drug than due to another etiology. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event may be consistent with a known pattern of drug (or drug class) effects; The drug seems more likely than other etiologies to cause the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; and/or The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)
Definitely related	The evidence is compelling that the study drug caused the adverse event. Guidelines: There is a reasonable temporal relationship of the event to the study drug; The event is consistent with a known pattern of drug (or drug class) effects; The drug is far more likely than other etiologies to have caused the effect; The adverse event diminished upon cessation of study drug exposure or reduction in dose; The adverse event worsened or recurred upon unintentional re-exposure to the study drug (Intentional rechallenge for the purpose of assigning causality should not be performed.)
Unknown	The data are inadequate to assign any of the above causal relationship categories to the study drug.

17.2 Adverse Event Grading

Adverse events will be graded according to the revised NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0).

If an AE is not listed in the NCI-CTCAE v.5.0, then the Physician will use the terms: mild, moderate, severe, life-threatening, or death to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Table 3.: Adverse Event Grade Definitions

GRADE		
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Fatal	Death related to AE

17.3 Handling of Serious Adverse Events

Adverse events classified as serious must be recorded on the AE page of the eCRF and require expeditious handling and reporting to the CRO Safety Surveillance, who will notify Redhill Biopharma in order for Redhill Biopharma to comply with regulatory requirements. These SAEs will include deaths, regardless of their causal relationship to investigational product. All SAEs must be reported using the Serious Adverse Event Report form. To the extent possible, the descriptive terminologies and other SAE attributes entered on the SAE report form should approximate similar information in the CRF. The completed SAE report form with supporting documentation must be provided to the sponsor within 24 hours of the study site personnel's initial notification/awareness of the event. All telephone communication regarding SAE must be followed by a written report. Duly authorized study site personnel may sign completed SAE report forms; however, it is recommended that the investigator sign each final SAE report.

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries, additional lab and test results, autopsy reports, etc.), should be collected subsequently, if not available at the time of the initial report, and immediately sent to the CRO using the same procedure as the initial SAE report. Information on the SAE must be in sufficient detail to allow for a complete medical assessment of the case and independent determination of causality.

For ease of analysis, worldwide standardization, and regulatory reporting, the sponsor will code each reported adverse event or symptom to its corresponding preferred term and body system/organ class in the MedDRA dictionary version adopted for the study. The principal investigator will be responsible for assessing severity based on the intensity of the event as it presented using the criteria listed in Section 17.2 Table 3.

All SAE reports must be sent to the CRO, who will notify the sponsor's medical monitor and the sponsor's regulatory/clinical affairs contact provided in a separate document.

As required, all investigators will be notified of all AE reports that are determined to be serious, unexpected, and related (by the reporting investigator or sponsor) to the investigational product. The notification will be in the form of a Safety Update (Dear Doctor Letter).

The notification is considered an addendum to the current Investigator's Brochure; therefore, upon receiving such notices, the investigator must review and immediately submit a copy to the IRB according to local regulations. The notification must be retained within the Investigator's Brochure. The investigator and IRB will determine if the informed consent requires revision.

17.4 Pregnancy

Pregnancy is not an adverse event but requires emergent reporting to the Sponsor. In case of a patient or patient's partner becoming pregnant during study participation, the pregnancy will be followed up to confinement and the neonatal period (30 days after delivery). Corresponding information will be filed with the source documents at the clinical site. Pregnancy should be reported in the same time period as SAE using the Pregnancy Form. If there are corresponding adverse events, these should be reported as separate AEs.

17.5 Laboratory Abnormalities

All new abnormal laboratory findings and those abnormal at baseline which change significantly (i.e., by at least one toxicity grade as defined in the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0) are considered AEs. Laboratory AEs for which there is no clinical intervention will be recorded only on the laboratory data pages of the eCRF. Laboratory AEs not listed in the NCI CTCAE v5.0 will be considered as grade 1 (mild) if there is no clinical effect or intervention. Laboratory values outside the normal range for certain parameters will not be considered AEs if they are generally not considered as indicating an abnormality; this includes such parameters as liver enzymes which are below the normal range. If there is a clinical sequela or intervention, the laboratory abnormality is to be graded according to the criteria used for clinical AEs, described above.

The NCI CTCAE v5.0 can be downloaded in pdf format at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

17.6 Other Safety Considerations

Patients will be followed for at least 28 days after discontinuation of study medication. When possible, the patient will come to the clinic for an in-person assessment. If not possible for logistic reasons, the assessment may be performed by phone contact with a study coordinator.

All AEs must be recorded and followed until resolution or for at least 28 days after discontinuation of study medication, whichever comes first.

Any clinically significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the AE page of the eCRF.

17.6.1 Serious Adverse Events

A written report of all SAEs that occur after the administration of study drug and during the study (ending with the safety follow-up visit, 28 days off-study drug) must be submitted to the IRB/ethics committee (EC) and the sponsor. SAEs/SUSARs must be reported to the Sponsor within 24 hours for a determination of expedited reporting to FDA. In all SAE reports, the investigator will advise whether or not the SAE is judged to be related to study drug administration. All SAEs that are judged by the investigator to be at least possibly related to study drug administration must be reported to the sponsor regardless of how much time has elapsed since the last exposure to study drug. All SAEs must be submitted to the IRB/EC in an annual report per local reporting guidelines.

17.6.2 Overdoses

Overdoses should be reported as a protocol violation. If an overdose results in an AE, the AE should be reported. If the overdose results in an SAE, then SAE reporting should be followed with overdose information entered in the narrative section. All available clinical information relevant to overdose, including signs and symptoms, laboratory findings, and therapeutic measures or treatments administered, should be summarized and discussed.

17.6.3 Adverse Events of Special Interest

Opaganib may cause neuropsychiatric toxicity that may be due to increases in ceramides.

In a Phase 1 healthy volunteer food effect study, these toxicities were found to be reduced by eating a light to moderate meal prior to each dose administration and this was likely due to delayed absorption and reduced Cmax.

Neuropsychiatric events reported in clinical studies to date include: hallucinations, anxiety, insomnia, lethargy, agitation, distress and dysarthria.

These neuropsychiatric adverse events occurred at higher frequencies at the highest dose administered, which is above the dose selected (best tolerated dose) for the current and future clinical studies.

The following adverse events are of special interest.

Patients who experience either of the following, at the discretion of the investigator, the medical monitor must be notified immediately (by phone or email), as feasible, but no longer than 24 hours:

- a sudden and clinically important increase in oxygen requirements
- a rapid decline in clinical status leading to intubation and mechanical ventilation
- clinically important increases in inflammatory markers

17.6.4 Data Safety Monitoring Board

A data safety monitoring board (DSMB) will be convened for the safety oversight of the study in order to assure safety of the trial participants.

The DSMB meetings to review the safety data, will be planned after 25%, 50% and 75% or when approximately 70, 135 and 200 randomized patients, respectively, have reached Day 7, and then Day 14.

Assessments will include but not be limited to:

a) all adverse events
b) all dose reductions in study drug

Ad hoc DSMB meetings will convene when clinically significant events (adverse events of special interest Section 17.5.3), per physician discretion, may indicate a potential increase in systemically important inflammation in any one patient in the study, based on an increased and clinically significant oxygen requirement, or a precipitous clinical deterioration that leads to intubation and mechanical ventilation.

At each review/meeting the DSMB will determine whether the study should proceed as planned or should be terminated.

No formal efficacy analysis will be performed at any DSMB review.

An interim analysis to determine futility will be conducted independent of the DSMB.

The DSMB will also be responsible for conveying the results of the futility analysis conducted by an independent unblinded statistician to the sponsor (futile/non-futile).

A DSMB charter will be provided as a separate document.

18 ETHICS

18.1 Investigator Responsibilities

18.1.1 Compliance with Declaration of Helsinki and Good Clinical Practices

The study will be performed in accordance with the Declaration of Helsinki (1964) as revised, most recently in Seoul (2008), US FDA regulations and the ICH Guideline for Good Clinical Practice, E6(R1). The investigator will ensure that all those concerned with conducting the study (such as pharmacists, research nurses and co-investigators) are provided with copies of the protocol and all safety information prior to the start of the study.

18.1.2 Institutional Review Board (IRB)/Ethics Committee (EC) Review and Approval

The investigator is responsible for obtaining IRB/EC approval to conduct this study (including IRB/EC approval of the Informed Consent form) and for ensuring continuing review as required by the IRB/EC. Written confirmation of this approval and periodic review must be provided to the sponsor prior to the start of the study and at appropriate intervals.

18.1.3 Informed Consent

The investigator will inform patients as to the nature, expected duration and purpose of the study, the administration of the study medication, and the hazards involved, as well as the potential benefits that may come from treatment with this investigational drug. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), and other national regulations, if study is conducted at sites outside the US.

The patient will be informed that his/her medical records will be subject to review by the sponsor and possibly by a representative of the Food and Drug Administration, as well as national regulatory authorities, for patients treated outside the US. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from this study at any time without prejudicing further care. Signed written informed consent must be obtained from every patient or legal representative prior to study entry. The original will be kept by the investigator and will be subject to review by the sponsor; a copy will be given to the patient.

18.1.4 Patient Anonymity

The anonymity of participating patients must be maintained. Patients will be identified by their initials and an assigned patient number on the datasheet, and other documents submitted to the sponsor, including but not limited to safety reports. Documents that will not be submitted to the sponsor and that identify the patient (e.g., the signed informed consent document), must be maintained in strict

confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, or sponsor representatives.

18.1.5 Confidentiality

All information provided to the investigator relevant to the study medication, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the sponsor, except as required by law.

18.1.6 Source Documentation

The investigator will allow inspections of the study site and documentation by clinical research and audit personnel from the sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to the subjects' medical or clinic records is necessary. The investigator will ensure that certain information is contained in the medical or clinic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories
- a note on the day the subject entered the study describing the study number, the drug being evaluated, the study number assigned to that subject and a statement that consent was obtained
- a note of each subsequent study visit including any concerns about adverse events or abnormal laboratory data and their resolution
- notes of all concomitant medication taken by the subject including start and stop dates
- a note of when the subject terminated from the study, the reason for termination and the subject's general condition at termination
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study (thereafter it will be archived with the study file)

18.1.7 Drug Accountability

The investigator agrees to supervise the maintenance of records of the receipt, dispensing and return or destruction of study material supplied by the sponsor. Destruction of any material must be witnessed and documented in writing. The dispensing record must make it clear which subject received which material.

18.1.8 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study center at regular intervals during the study for monitoring purposes and to assist the research staff with any queries they may have.

18.1.9 Case Report Forms, Investigator's Study File and Record Retention

All case report forms and supporting source documentation must be available to the sponsor during monitoring visits.

Prior to review of the case report forms by the sponsor's representative and forwarding of the case report forms to the sponsor, they should be reviewed for completeness and legibility by the investigator or a member of the research team.

The investigator will maintain all records relating to the study (including copies of case report forms) for at least 2 years after written notification by the sponsor that the investigational drug program has been either completed or terminated, or that a New Drug Application (NDA) has been approved by the FDA. Should the investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the study records, custody must be transferred to a person who will accept that responsibility, and the sponsor must be notified in writing of the name and address of said person.

18.1.10 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this study without the prior written permission of the subject, the sponsor and the IRB.

18.2 Sponsor Responsibilities

18.2.1 General

The sponsor agrees to adhere to US FDA Guidelines on Good Clinical (Research) Practices and with the ICH Guideline for Good Clinical Practice, E6(R1). The sponsor has a legal responsibility to report fully to regulatory authorities the results of this study. It is the sponsor's responsibility to obtain appropriate regulatory approval to perform the study.

18.2.2 Case Report Forms

Case report forms will be provided by the sponsor or, upon agreement with the sponsor, forms generated by the investigative site may be used. If an electronic data collection system is used, the system will be compliant with applicable aspects of 21 CRF Part 11, ICH guidelines, GCP and HIPAA.

18.2.3 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study center at regular intervals during the study for monitoring purposes and to assist the research staff with any queries they may have. Case report forms and source documentation will be available for review during monitoring visits to the center. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and good clinical (research) practice obligations, proper maintenance of records including drug accountability records, correct administration of study medications including storage conditions and accurate reporting of adverse events.

18.2.4 Audit

The sponsor has an obligation to audit a proportion of studies; this is usually undertaken by a department other than the clinical research department. Therefore the sponsor, an independent auditor or a regulatory authority may wish to audit the study site and documentation and these audits may take place as the study is running or up to several years later.

18.2.5 Confidentiality

The sponsor will not keep any material on file bearing any subject's name, and the subject's confidentiality will be maintained at all times.

18.2.6 Protocol Modifications

If necessary during the course of the study, the protocol may be modified by the sponsor in consultation with the investigator. Except in the case of modifications to resolve an imminent safety issue, any protocol modification or revision must be reviewed and approved by the investigator's IRB/EC prior to implementation.

18.2.7 Publication

RedHill Biopharma will provide unblinded data to a publications committee for publication of the results of this study once completed and all data have been cleaned and the blind broken. The publications committee will be constituted according to the guidelines developed by the Company. If deemed necessary by the Company for protection of proprietary information prior to patent filing, the investigator agrees to delay for 60 days before any presentation or publication is submitted.

19 STATISTICAL METHODS

This section of the protocol describes the statistical analysis as it is foreseen at the time of planning the study. A fully detailed Statistical Analysis Plan (SAP) will be produced and finalized after finalizing the protocol and before breaking the blind of the study. A supplementary document will provide further details regarding the planned futility analysis.

19.1 Sample Size Considerations

It is planned to enroll approximately 270 eligible patients into the double-blind treatment phase, to receive either opaganib added to standard of care (n=135), or matching placebo added to standard of care (n=135). The sample size calculation was based on powering the study with respect to the primary analysis of the primary efficacy endpoint of proportions of patients requiring intubation and mechanical ventilation at 14 days (refer to section 15.1). It was assumed that the treatment failure (mechanical ventilation rate at 14 days in the control arm would be 25% and that opaganib is expected to provide absolute 15% reduction of this rate, to a failure rate of 10%. A total of 270 subjects provides 90% power to detect the assumed difference in failure rate, using chi square test, at a two-sided α=0.05 level of significance. This sample size calculation takes into account a planned futility analysis to be performed after the first 100 patients in the study have been evaluated for the primary endpoint.

19.2 Stratification

Patients will be stratified based on patients meeting three or more high risk parameters for COVID-19 outcomes at baseline (yes or no). The parameters are: 1) age at screening, ≥60 years of age, (yes or no); 2) male, (yes or no); 3) HbA1c at screening, ≥6.5 (yes or no); 4) hypoxemia without commensurate increased work of breathing (defined as increased respiratory rate, nasal flaring and/or increase use of respiratory muscles including the diaphragm [yes or no]); 5) known underlying chronic lung disease (yes or no); 6) known cardiovascular disease or hypertension (yes or no); 7) BMI ≥ 28.0 kg/m^2 (yes or no); 8) known renal disease (yes or no).

19.3 Analysis of the Primary Efficacy Endpoint

The primary analysis will be based on a composite failure (Yes/No) variable, indicating if a subject had required intubation and mechanical ventilation or had died by study Day 14.

In the rare case of unknown patient outcome (patient lost to follow up), it will also be counted as treatment failure for the primary analysis. If a patient initiates new investigational therapy for COVID-19 within 14 days, this will also be regarded, in the primary analysis, as treatment failure.

The number and percentages of subjects with failure event will be tabulated per treatment group. A 95% confidence interval will be constructed for each proportion. A Cochran Mantel-Haenzel (CMH)

test will compare the proportion of failure between the two groups, using the study stratification factors used for randomization, and corresponding risk difference estimate will be presented with 95% confidence interval. Exact confidence intervals will be used as needed.

The significance level for this test will be two-sided 5%. In the case of small number of events (less than 5 events in any study arm), the Fisher exact test will be used.

The number and percent of each of the failure types (intubation and mechanical ventilation) will be described by group.

The primary analysis will be based on the modified Intent to treat population (mITT), which consist of all patients that were randomized and treated with at least one dose of study drug,

Sensitivity and supportive analyses for the primary endpoint analysis will be defined and detailed in the statistical analysis plan. These will address the following aspects:

- Using an Intention-To-Treat population as well as Per-Protocol (PP) population. Criteria for PP protocol will be based on inclusion and exclusion criteria and protocol violations during the study and will be defined before database lock.
- To account for the possibility of errors in values of stratification factors used for randomization, the primary analysis will supportively be repeated using the correct values.
- Difference between the treatment and control groups when controlling for possible imbalance in important baseline factors will be analysed by evaluating the odds ratio obtained from estimating a multiple logistic regression model. The list of baseline variables will be finalized in the SAP.

Sensitivity analysis for the imputation of missing data.

19.4 Analysis of the Secondary Efficacy Endpoints

In general, binary variables will be analyzed using similar methods as those specified for the primary endpoint. In case loss to follow-up before event will be recorded, the Cumulative Incidence probabilities at study day 14 will be estimated using time to event analysis, censoring loss-to follow up patients at last valid observation date. This analysis will treat death before event of interest as competing event.

Time to event endpoints will be calculated as the number of days from study day 1 until the event of interest or last valid observation time, whichever occurs first. A patient for whom event of interest will not be observed will be regarded as right censored. The time frame for all these endpoints is from Day 1 until end of off-study-drug follow-up. Additional analysis will be performed in the time frame of the 14-day-treatment DB Phase period (sensitivity analysis).

Time to event endpoints will be compared using the stratified Log-rank test and the stratified Cox proportional hazards regression model will be used to estimate the hazard ratio (HR) along with 95% confidence interval, comparing opaganib versus control group. Kaplan-Meier plot by treatment arm will be presented, and when death is considered competing risk for the event of interest, Cumulative Incidence Function (CIF) plots will be presented as well.

The endpoint total oxygen requirement (area under the curve) using the daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14) will be calculated for each subject using the trapezoidal rule after subtracting the baseline oxygen requirement at each day. Days where no supplementary oxygen was needed, will be recorded as 0, including days after patient discharge, if hospital discharge occurs prior to Day 14. If several values of oxygen requirement (L/min) are recorded in a certain day, the highest of these values will be taken. For patients require intubation and mechanical ventilation at certain days, missing values will be assigned the maximal supplemental oxygen flow requirement of 60L/min for those days. Patients who die before day 14, will also be assigned this maximal requirement through day 14 from day of death. In case that all supplemental oxygen values are missing while subject still requires supplemental oxygen (before day 14), the last value carried forward - until Day 14, or death, if occurred before, will be implemented.

Descriptive statistics of the baseline-adjusted AUC will be presented by group along with 95% confidence interval for the difference in means between the groups. Analysis of covariance will be used to test for difference in group means, adjusting to baseline value and stratification variables.

A sensitivity analysis to the missing data handling approach will be performed using an AUC summary statistics approach, in which groups AUC is calculated from the estimated parameters of a Repeated-Measures model.

To note, as flow units will vary between low flow and high flow supplemental oxygenation, an algorithm will be developed to address that. Analyses of endpoints depending on this measurement will be performed on the transformed data.

All secondary endpoints analyses will be based on mITT population.

19.5 Safety Analyses

The safety and tolerability of opaganib will be determined by reported treatment emergent adverse events (TEAEs), physical examinations, vital signs, and laboratory tests. Patients who receive at least one dose of study drug are considered evaluable for safety (Safety population).

Detailed specification of the safety analyses will be provided in the SAP.

19.6 Type 1 error control

The overall study-wise type I error will be 5%. The non-binding futility analysis does not increase type 1 error probability and thus does not impact final analysis significance level (Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics, November 2019).

To protect the study from type I error inflation, the secondary efficacy endpoints will be interpreted inferentially only if a statistically significant treatment effect (p-value ≤0.05) is detected in the primary endpoint. Type I error will be further controlled by employing Hierarchical Approach within the secondary efficacy endpoints: each endpoint will be formally analyzed only in case the previous endpoint will be statistically significant (p-value ≤0.05).

19.7 Interim Analysis

An unblinded futility interim analysis will be conducted when approximately 100 subjects (approximately 50 subjects from each group) have been evaluated for the primary endpoint to determine the probability of rejecting the null hypothesis of no effect and if it would be futile to continue the study. Criteria will be prospectively determined and documented in the final version of the Statistical Analysis Plan (SAP) prior to the interim analysis. The analysis will be conducted by an independent unblinded statistician who will inform the DMC of the futility outcome. Strict procedures will be employed to maintain the confidentiality of the interim results. To safeguard study integrity, the pre-defined details of the stopping rules are documented separately and will be part of the DMC charter.

20 INVESTIGATOR'S STATEMENT

I have read the protocol entitled "Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2/3 Study, in Adult Subjects Hospitalized with Severe to Critical SARS-CoV-2 Positive Pneumonia" and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information provided by Redhill Biopharma to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the drug and the study. I understand that the study may be terminated or enrollment suspended at any time by Redhill Biopharma, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

Signature of Investigator	Date (day/month/year)
Printed Name of Investigator	Site Number

21 REFERENCES

Yifei Chen, Liangjun Chen, Qiaoling Deng, Guqin Zhang, Kaisong Wu, Lan Ni1, Yibin Yang, Bing Liu, Wei Wang, Chaojie Wei, Jiong Yang, Guangming Ye, Zhenshun Cheng, The Presence of SARS-CoV-2 RNA in Feces of COVID-19, ORCID iD: 0000-0002-7387-496X

Dai L, Plaisance-Bonstaff K, Voelkel-Johnson C, Smith CD, Ogretmen B, Qin Z, Parsons. Sphingosine kinase-2 maintains viral latency and survival for KSHV-infected endothelial cells. PLoS One. 2014 Jul 10;9(7):e102314.

Ebenezer DL, Berdyshev EV, Bronova IA, Liu Y, Tiruppathi C, Komarova Y, Benevolenskaya EV, Suryadevara V, Ha AW, Harijith A, Tuder RM, Natarajan V, Fu P. Pseudomonas aeruginosa stimulates nuclear sphingosine-1-phosphate generation and epigenetic regulation of lung inflammatory injury. Thorax. 2019 Jun;74(6):579-591.

French KJ, Zhuang Y, Maines LW, Gao P, Wang W, Beljanski V, Upson JJ, Green CL, Keller SN, Smith CD. Pharmacology and antitumor activity of ABC294640, a selective inhibitor of sphingosine kinase-2. J Pharmacol Exp Ther. 2010 Apr;333(1):129-39.

Liu Q, Rehman H, Shi Y, Krishnasamy Y, Lemasters JJ, Smith CD, Zhong Z. Inhibition of Sphingosine Kinase-2 Suppresses Inflammation and Attenuates Graft Injury after Liver Transplantation in Rats. PLoS One. 2012;7(7):e41834.

Maines LW, Fitzpatrick LR, French KJ, et al. Suppression of ulcerative colitis in mice by orally-available inhibitors of sphingosine kinase. Dig Dis Sci. 2008; 53(4):997-1012.

Maines LW, Fitzpatrick LR, Green CL, Zhuang Y, Smith CD. Efficacy of a novel sphingosine kinase inhibitor in experimental Crohn's disease. Inflammopharmacology. 2010 Apr; 18(2):73-85

Reid, S.P.; Tritsch, S.R.; Kota, K.; Chiang, C.-Y.; Dong, L.; Kenny, T.; Brueggemann, E.E.; Ward, M.D.; Cazares, L.H.; Bavari, S. Sphingosine kinase 2 is a chikungunya virus host factor co-localized with the viral replication complex. Emerg. Microbes Infect. 2015, 4, e61

van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020 Mar 17.

Wilson KC, Chotirmall SH, Bai C, Rello J. COVID-19: Interim Guidance on Management Pending Empirical Evidence. Last updated April 3, 2020. www.thoracic.org/professionals/clinicalresources/disease-related-resources/covid-19-guidance.pdf.

World Health Organization. WHO R&D Blueprint: novel coronavirus. 2020. Downloaded 3/20/20: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf?ua=1

Xia C, Seo YJ, Studstill CJ, Vijayan M, Wolf JJ, Hahm B. Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. Antiviral Res. 2018 Oct;1 58:171-177.

Yamane D, McGivern DR, Wauthier E, Yi M, Madden VJ, Welsch C, Antes I, Wen Y, Chugh PE, McGee CE, Widman DG, Misumi I, Bandyopadhyay S, Kim S, Shimakami T, Oikawa T, Whitmire JK, Heise MT, Dittmer DP, Kao CC, Pitson SM, Merrill AH Jr, Reid LM, Lemon SM. Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation. Nat Med. 2014 Aug;20(8):927-35.

Zhou C, Gao C, Xie Y, Xu M. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 2020 Mar 9.

Appendix 1 WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8