**COVER PAGE for ABC-110 STUDY PROTOCOL**

The following document is the study protocol of:

Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2a Study in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia

Dated 30 Aug 2020

NCT04414618

# CLINICAL STUDY PROTOCOL: ABC-110

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| Title: | Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2a Study, in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia |
| Name of Investigational Product: | Opaganib (ABC294640) |
| Phase of Development: | Phase 2a/Proof of Concept |
| IND number: | 148560 |
| Protocol Identification: | ABC-110 |
| Sponsor Name and Address: | RedHill Biopharma Ltd.<br>21 Ha'arba'a St.<br>Tel-Aviv 6473921, Israel<br>Tel: +972 (0)3 541 3131<br>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. |
| Date of Protocol Amendment: | Version 1.2, 30 August 2020<br>Version 1.1, 6 May 2020<br>Version 1.0, 16 April 2020 |
| Name:<br>Title:<br>Phone: | _____<br>Signature |

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**Approvals**

Sponsor Representatives

_____ _____

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

_____ _____

Mark L. Levitt MD PhD Date
Medical Monitor

# 2 PROTOCOL SYNOPSIS

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|---|---|
| **Study Title** | Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia: a Randomized, Double-blind, Placebo-Controlled Phase 2a Study, in Adult Subjects Hospitalized with SARS-CoV-2 Positive Pneumonia |
| **Protocol Number** | ABC-110 |
| **Sponsor** | RedHill Biopharma Ltd. |
| **Investigational Product** | Opaganib (ABC294640) |
| **Primary Objective** | 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) |
| **Secondary Objectives** | 1) To evaluate the time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min<br>2) To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14<br>3) To evaluate the proportion of afebrile patients at Day 14<br>4) To evaluate the time to negative swabs for SARS-CoV-2 by PCR<br>5) To evaluate the proportion of patients with negative swabs for SARS-CoV-2 by PCR at Day 14<br>6) To evaluate the need for intubation and mechanical ventilation by Day 14<br>7) To evaluate the time to mechanical ventilation<br>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<br>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) |

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| **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 COVID-19 pneumonia |
| **Study Population** | The study population will consist of patients diagnosed with COVID-19 infection who have developed pneumonia defined as radiographic opacities on chest X-ray and require supplemental oxygen. The patients must be hospitalized at least during screening and at baseline (Day 1). |
| **Study Design and Description** | This is a phase 2a, proof of concept, multi-center randomized double-blind, parallel arm, placebo-controlled study. The study is planned be performed in US and in other countries, in approximately 15 clinical sites.<br><br>After informed consent is obtained, patients will enter a screening phase for no more than 3 days, to determine eligibility. Approximately 40 eligible patients will be randomized to 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 there is currently no consensus for a definitive treatment specifically targeting the SARS-CoV-2 virus causing COVID-19 (Wilson, 2020), standard of care will refer to regional, institutional or physician directed therapies, that may be implemented during the COVID-19 pandemic.<br><br>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 and/or supportive). Study drug will be administered every day for 14 days (Day 1 to Day 14), unless the patient has been discharged from the hospital without requiring supplemental oxygen, in which case study drug will only be administered to Day 10.<br><br>All participants will be followed up for 4 weeks after their last dose of study drug, which may occur at the end of the 2-week double-blind treatment phase or after premature study drug discontinuation, based upon patient or physician determination. |
| **Stratification** | Patients will be stratified based on a minimization algorithm taking the following three parameters into account: age at screening, ≥70 years of age, (yes or no); HbA1c at screening, ≥6.5, (yes or no); oxygen requirement at baseline, requiring non-invasive positive pressure ventilation (e.g. via BIPAP, CPAP), (yes or no) |
| **Treatment** | Opaganib 500 mg Q12 hour or matching placebo |

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| **Study Duration** | Recruitment period is estimated at 3 months<br><br>The maximum duration of study participation will be up to 45 days (including up to 3 days screening; 2 weeks double-blind (DB) treatment phase and 4-weeks off-study drug follow-up) |
| **Eligibility Criteria** | ***Inclusion:***<br><br>1) Adult male or female ≥18 to ≤80 years of age<br><br>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<br><br>3) The patient requires supplemental oxygen at baseline<br><br>4) The patient, guardian or legal representative has signed a written IRB-approved informed consent<br><br>5) Male participants with female partners of child-bearing potential agree to one of the following methods of contraception during the treatment period and for at least 1 month after the last dose of study drug:<br>• Abstinence from penile-vaginal intercourse and agree to remain abstinent.<br>• Male condom, with female partner using a highly effective contraceptive method. (For further details regarding highly effective contraceptive methods please see section 9.3.)<br><br>In addition, male participants must refrain from donating sperm for the duration of the study and for 1 months after last dose of study drug.<br><br>Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for at least 1 months after the last dose of study drug<br>Female participants:<br>A female participant is eligible to participate if she is:<br>a) not pregnant<br>b) not breastfeeding<br>c) not a woman of child-bearing potential (WOCBP, as defined in Section 9.3)<br>d) a WOCBP who agrees to use a highly effective method of contraception consistently and correctly during the treatment period and for at least 1 months after the last dose of study drug (please see further details on Section 9.3).<br><br>***Exclusion:*** |

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| | 1. Any co-morbidity that may add risk to the treatment in the judgement of the investigator.<br>2. Requiring intubation and mechanical ventilation<br>3. Patient having a do not intubate or do not resuscitate order<br>4. Oxygen saturation ≥95% on room air<br>5. Any preexisting respiratory condition that requires intermittent or continuous ambulatory oxygen prior to hospitalization<br>6. Patient is, in the investigator's clinical judgement, unlikely to survive >72 hours<br>7. Pregnant (positive serum test within 3 days prior to randomization) or nursing women<br>8. Unwillingness or inability to comply with procedures required in this protocol.<br>9. Corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms for females or >450 ms for males, calculated using Friedericia's formula (QTcF)<br>10. AST (SGOT) or ALT (SGPT) > 5.0 x upper limit of normal (ULN)<br>11. Bilirubin >2.0 x ULN (except where bilirubin increase is due to Gilbert's Syndrome)<br>12. Serum creatinine >2.0 X ULN<br>13. Absolute neutrophil count <1000 cells/$mm^3$<br>14. Platelet count <75,000/$mm^3$<br>15. Hemoglobin <8.0 g/dL<br>16. Currently taking medications that are sensitive CYP3A4, CYP1A2, CYP2C9, CYP2C19 or CYP2D6 substrates and have a narrow therapeutic index. These should be decided in discussion with the Medical Monitor on a case-by-case basis.<br>17. Currently taking medications that are strong inducers or inhibitors of CYP2D6 and CYP3A4. These should be decided in discussion with the Medical Monitor on a case-by-case basis.<br>18. Currently taking warfarin, apixaban, argatroban or rivaroxaban.<br>19. Current drug or alcohol abuse |

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| | 20. Currently participating in a clinical study assessing pharmacological treatments, including anti-viral studies |
| **Number of Subjects** | Up to approximately 40 subjects will be randomized |
| **Number of Investigator Sites** | Approximately 15 participating hospital centers |
| **Screening/Baseline Assessments** | • Signed informed consent<br>• Eligibility determination<br>• Complete medical history (including onset of COVID-19 symptoms)<br>• Concomitant medication assessment<br>• Baseline review of systems<br>• Physical examination<br>• Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter)<br>• Weight if the patient is ambulatory<br>• Oxygen requirement (L/min)<br>• 12-lead electrocardiogram<br>• Chest Xray<br>• Nasopharyngeal or oropharyngeal swab for SARS-CoV-2 PCR test<br>• Serum chemistry<br>• CRP, D-Dimer, LDH, ferritin, cardiac troponin<br>• HbA1c<br>• CBC with differential<br>• Urinalysis |

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| | • Serum 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:<br>• Concomitant medications<br>• Adverse Events<br>• Interim Physical exam<br>• Vital signs (temperature, blood pressure, pulse rate, respiratory rate and oxygen saturation by pulse oximeter)<br>• Oxygen requirement (L/min)<br>The following will be monitored less frequently as part of standard of care and wherever possible:<br>• For patients on concomitant hydroxychloroquine, 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 10, 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<br>• Nasopharyngeal or oropharyngeal viral swab for SARS-CoV-2 PCR test every 1-3 days<br>• Serum chemistry once weekly<br>• Serum CRP, D-Dimer, LDH, ferritin, cardiac troponin once weekly<br>• CBC with differential once weekly<br>• Chest X-ray as per physician decision |
| **Study Endpoints** | **Primary**<br>The total oxygen requirement (area under the curve) using the daily supplemental oxygen flow (L/min) over 14 days (Day 1 to Day 14)<br>**Secondary**<br>1) Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min |

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| | 2) The percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14<br>3) The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart<br>4) The percentage of patients with at least two consecutive negative swabs, followed by continued negative swabs, for SARS-CoV-2 by PCR at Day 14<br>5) The percentage of patients requiring intubation and mechanical ventilation by the end of the 2-week off-study-drug follow-up<br>6) The time to intubation and mechanical ventilation<br>7) 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<br>8) Mortality due to any cause at Day 30<br>**Exploratory**<br>1) 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<br>**Safety**<br>1) Incidence rates of all treatment-emergent AEs (TEAEs) and SAEs<br>2) Evaluation of vital signs<br>3) Evaluation of laboratory parameters (chemistry and hematology)<br>4) Evaluation of electrocardiograms (ECG) |
| **Sample Size Estimation** | The sample size for this Proof of Concept study was not chosen for statistical consideration, as there are no formal statistical inferences planned. The size of the study is judged adequate for the preliminary evaluation objectives. |
| **Statistical Methods** | The primary efficacy objective of the study is to evaluate the effect of Opaganib on total supplemental oxygen requirement (area under the curve) using daily oxygen flow (L/min) measurements for 14 days (Day 1 to Day 14). The primary efficacy endpoint will calculate for each patient the area under the curve of the supplemental oxygen requirement through day 14, 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. If several values of |

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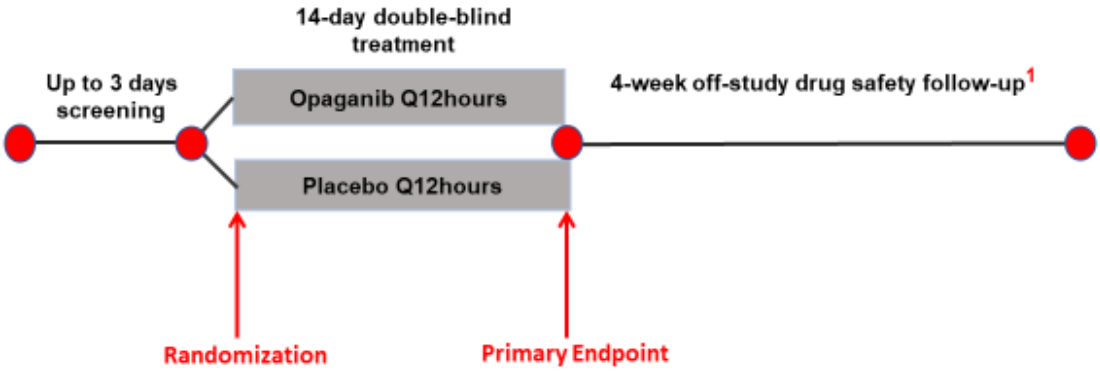
| | oxygen requirement (L/min) are recorded in a certain day, for the primary analysis the highest of these values will be taken. In the primary analysis, for patients who die before Day 14, or require intubation and mechanical ventilation, missing daily values will be assigned the maximal supplemental oxygen flow requirement of 8L/min. For patients discharged from hospital on supplemental oxygen prior to Day 14, if no values are collected by the site after discharge, the oxygen requirement (L/min) on the day of discharge will be assigned thereafter for each day to Day 14. 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, Descriptive statistics of the baseline-adjusted AUC will be presented by group along with 95% confidence interval for each group and for the difference in means between the groups. It is planned to collect supplemental oxygen requirement up to Day 14 even if a patient discontinues treatment prior to Day 14 but continues in the study to Day 14. Further, it is assumed that loss to follow up such that vital status up to Day 14 will be missing is unlikely. Therefore, the primary analysis will assume that in case that all supplemental oxygen values are missing after treatment discontinuation, the last value is carried forward - until Day 14, or death, if occurred before. A sensitivity analysis to the above 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. |

# 3 STUDY SCHEMATIC




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

# 4 SCHEDULE OF ASSESSMENTS

*Table 1 Schedule of Assessments for the Study*

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

[1] 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)

[2] record weight if patient is ambulatory

[3] pharyngeal samples for SARS-CoV-2 PCR are collected daily, per standard of care. For patients having nasopharyngeal swabs, the same nostril must be used during the study

[4] for patients on concomitant hydroxychloroquine, the 12-lead ECG will be repeated after 3 hours (±30mins) of initial dose, on Day 2 and Day 4

[5] Chest X-ray, lab draws will be at the discretion of the Investigator depending on patient clinical condition

[6] CRP=C-reactive protein, LDH=lactate dehydrogenase

[7] women of childbearing potential; serum pregnancy test must be negative within 3 days prior to randomization

# 5 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 |
| CHKV | Chikungunya virus |
| CRO | Clinical Research Organization |
| CYP | Cytochrome P450 |
| DB | Double-blind |
| 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 |
| 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 |

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| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment Emergent Adverse Event |
| ULN | Upper limit of the normal range |
| WHO | World Health Organization |
| WOCBP | Women of childbearing potential |

# 6 BACKGROUND INFORMATION

## 6.1 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.

## 6.2 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).

## 6.3 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 remarkable 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.

## 6.4 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.

### 6.4.1 Completed Studies

#### 6.4.1.1 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.

#### 6.4.1.2 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.

#### 6.4.1.3 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 STUDY OBJECTIVES

## 7.1 Primary

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)

## 7.2 Secondary

1) To evaluate the time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min
2) To evaluate the proportion of patients no longer requiring supplemental oxygen for at least 24 hours by Day 14
3) To evaluate the proportion of afebrile patients at Day 14
4) To evaluate the time to negative swabs for SARS-CoV-2 by PCR
5) To evaluate the proportion of patients with negative swabs for SARS-CoV-2 by PCR at Day 14
6) To evaluate the need for intubation and mechanical ventilation by Day 14
7) To evaluate the time to mechanical ventilation
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

## 7.3 Exploratory

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

## 7.4 Safety

To assess the safety and tolerability of opaganib administered orally at 500 mg Q 12 hours, for up to 4 weeks, in patients with COVID-19 pneumonia.

# 8 STUDY POPULATION

The study population will consist of patients diagnosed with COVID-19 infection who have developed pneumonia defined as radiographic opacities on chest X-ray, and require supplemental oxygen. The patients must be hospitalized at least during screening and at baseline (Day 1).

# 9 ELIGIBILITY CRITERIA

## 9.1 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
3) The patient requires supplemental oxygen at baseline
4) The patient, guardian or legal representative has signed a written IRB-approved informed consent
5) Male participants with female partners of child-bearing potential agree to one of the following methods of contraception during the treatment period and for at least 1 month after the last dose of study drug:
   - Abstinence from penile-vaginal intercourse and agree to remain abstinent.
   - Male condom, with female partner using a highly effective contraceptive method. (For further details regarding highly effective contraceptive methods please see section 9.3.)

In addition male participants must refrain from donating sperm for the duration of the study and for 1 months after last dose of study drug.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for at least 1 months after the last dose of study drug
Female participants:
A female participant is eligible to participate if she is:

d) not pregnant
e) not breastfeeding
f) not a woman of child-bearing potential (as defined in Section 9.3)
d) a WOCBP who agrees to use a highly effective method of contraception consistently and correctly during the treatment period and for at least 1 months after the last dose of study drug (please see further details on Section 9.3).

## 9.2 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) Patient having a do not intubate or do not resuscitate order
4) Oxygen saturation >95% on room air

5) Any preexisting respiratory condition that requires intermittent or continuous ambulatory oxygen prior to hospitalization
6) Patient is, in the investigator's clinical judgement, unlikely to survive >72 hours
7) Pregnant (positive serum test within 3 days prior to randomization) or nursing women
8) Unwillingness or inability to comply with procedures required in this protocol.
9) Corrected QT (QTc) interval on electrocardiogram (ECG) >470 ms for females or >450 ms for males, calculated using Friedericia's formula (QTcF)
10) AST (SGOT) or ALT (SGPT) > 5 x upper limit of normal (ULN)
11) Bilirubin >2x ULN (except where bilirubin increase is due to Gilbert's Syndrome)
12) Serum creatinine >2.0 X ULN
13) Absolute neutrophil count <1000 cells/$mm^3$
14) Platelet count <75,000/$mm^3$
15) Hemoglobin <8.0 g/dL
16) Currently taking medications that are sensitive CYP3A4, CYP1A2, CYP2C9, CYP2C19 or CYP2D6 substrates and have a narrow therapeutic index. These should be decided in discussion with the Medical Monitor on a case-by-case basis.
17) Currently taking medications that are strong inducers or inhibitors of CYP2D6 and CYP3A4. These should be decided in discussion with the Medical Monitor on a case-by-case basis.
18) Currently taking warfarin, apixaban, argatroban or rivaroxaban
19) Current drug or alcohol abuse
20) Currently participating in a clinical study assessing pharmacological treatments, including anti-viral studies

## 9.3 Women of Childbearing Potential Definition

For the purpose of this protocol, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche, and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, tubal ligation and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, multiple FSH measurement are required to confirm postmenopausal state.

Highly effective contraceptive measures, with a failure rate of less than 1% per year, for WOCBP include:

a. intrauterine device

b. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)

c. and/or sexual abstinence.

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

d. If combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable), intrauterine hormone-releasing system associated with inhibition of ovulation is utilized then a secondary method of highly effective birth control is required, for example condom plus spermicide, or cervical cap plus spermicide.

Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods.

# 10 STUDY DESIGN

## 10.1 Overall Investigation Plan

This is a phase 2a, proof of concept, multi-center randomized double-blind, parallel arm, placebo controlled study. The study is planned be performed in the US and in other countries, in approximately 15 clinical sites.

After informed consent is obtained, patients will enter a screening phase for no more than 3 days, to determine eligibility. Approximately 40 eligible patients will be randomized to 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 there is currently no consensus for a definitive treatment specifically targeting the SARS-CoV-2 virus causing COVID-19 (K. Wilson, 2020), standard of care will refer to regional, institutional or physician directed therapies, that may be implemented during the COVID-19 pandemic.

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 and/or supportive). Study drug will be administered every day for 14 days (Day 1 to Day 14), unless the patient has been discharged from the hospital without requiring supplemental oxygen, in which case study drug will only be administered to Day 10.

All participants will be followed up for 4 weeks after their last dose of study drug, which may occur at the end of the 2-week double-blind treatment phase or after premature study drug discontinuation, based upon patient or physician determination.

The maximum duration of study participation will be 45 days (including up to 3 days screening; 2 weeks double-blind (DB) phase and 4-weeks off-study drug follow-up).

## 10.2 Study Assessments

The assessments for this study are listed in Section 12.0

## 10.3 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
- The patient has experienced an AE that meets protocol defined stopping criteria (refer to Section 10.5.2)
- AEs or adverse device effects (ADEs) based on the judgment of the InvestigatorThe 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.

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

## 10.4 Study Drug Information and Dosage

### 10.4.1 Identification and Description of Investigational Drug

Opaganib is supplied as Capsules 250 mg, containing 250 mg opaganib along with excipients in white opaque hard gelatin capsules.

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

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

For the treatment phase of the study, treatments will be blinded.

### 10.4.2 Packaging and Labeling

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

The labels will include:

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 room temperature 15-30°C (59-86°F)

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

Lot number

Manufacturing date in day/month/year format.

### 10.4.3 Storage and Handling of Investigational Drug

Study drug should be stored at room temperature 15-30°C (59-86°F)

## 10.5 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.

### 10.5.1 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 2-week off-study drug safety follow-up period

| NCI CTC 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. The physician should discuss with the sponsor opaganib-related Grade 2 or greater toxicities that are likely to result in study drug discontinuation. Please see criteria for stopping study drug in section 10.5.2). |
| Any ≥ Grade 2 toxicity (specifically neuropsychiatric) | The physician should discuss with the sponsor opaganib-related Grade 2 or greater toxicities that are likely to result in study drug discontinuation. Please see criteria for stopping study drug in section 10.5.2). |

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

### 10.5.2 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 15.2 Table 3 for Adverse Event Grade Definitions):

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

# 11 PRIOR AND CONCOMITANT MEDICATIONS

## 11.1.1 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.

## 11.1.2 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.

## 11.1.3 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.

## 11.1.4 Prohibited Medications

Medications that are sensitive CYP3A4, CYP1A2 CYP2C9, CYP2C19 or CYP2D6 substrates and have a narrow therapeutic index are prohibited. These should be decided in discussion with the Medical Monitor on a case-by-case basis.

Strong inducers or inhibitors of CYP2D6 and 3A4 are prohibited. These should be decided in discussion with the Medical Monitor on a case-by-case basis.

Warfarin, apixaban, argatroban and rivaroxaban are prohibited

# 12 SCHEDULE OF EVENTS

## 12.1.1 Procedures and Assessments

Please see "Schedule of Assessments" for a detailed study schedule (Section 4) presented in tabular form.

## 12.1.2 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 -7 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)
- 12-lead electrocardiogram
- Chest Xray
- Nasopharyngeal or pharyngeal swab for SARS-CoV-2-PRC
- Serum chemistry
- CRP, D-Dimer, LDH, ferritin, cardiac troponin
- CBC with differential
- Urinalysis
- Serum pregnancy test (for women of childbearing potential) within 3 days prior to treatment

## 12.1.3 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)

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

- For patients on concomitant hydroxychloroquine, 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, 28 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
- CBC with differential once weekly
- Chest X-ray as per physician decision

### 12.1.5 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)

# 13 STUDY ENDPOINTS

## 13.1 Primary

The total oxygen requirement (area under the curve) using the daily oxygen flow (L/min) over 14 days (Day 1 to Day 14)

## 13.2 Secondary

1) Time to 50% reduction from baseline in supplemental oxygen based on oxygen flow in L/min
2) The percentage of patients no longer receiving supplemental oxygen for at least 24 hours by Day 14
3) The time to two consecutive negative swabs for SARS-CoV-2 by PCR, at least 24 hours apart
4) The percentage of patients with at least two consecutive negative swabs, followed by continued negative swabs, for SARS-CoV-2 by PCR at Day 14
5) The percentage of patients requiring intubation and mechanical ventilation by the end of the 2-week off-study-drug follow-up
6) The time to intubation and mechanical ventilation
7) 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
8) Mortality due to any cause at Day 30

## 13.3 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

## 13.4 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)

# 14 SAFETY REPORTING

All adverse events should be reported from first dose 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 a Serious Adverse Event report form and provide any supporting documentation to the Medical Monitor at the Fax number or email provided above.

To discuss SAE with Medical Monitor, contact him directly by phone at the numbers provided above.

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.

# 15 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.

## 15.1 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.<br>Guidelines:<br>There is no reasonable temporal relationship of the event to the administration of drug;<br>The pattern is inconsistent with that known for the drug; and/or<br>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.<br>Guidelines:<br>There is no reasonable temporal relationship of the event to the administration of drug;<br>The pattern is inconsistent with that known for the drug; and/or<br>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.<br>Guidelines:<br>There is a reasonable temporal relationship of the event to the study drug;<br>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.<br>Guidelines:<br>There is a reasonable temporal relationship of the event to the study drug;<br>The event may be consistent with a known pattern of drug (or drug class) effects;<br>The drug seems more likely than other etiologies to cause the effect;<br>The adverse event diminished upon cessation of study drug exposure or reduction in dose; and/or<br>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.<br>Guidelines:<br>There is a reasonable temporal relationship of the event to the study drug;<br>The event is consistent with a known pattern of drug (or drug class) effects;<br>The drug is far more likely than other etiologies to have caused the effect;<br>The adverse event diminished upon cessation of study drug exposure or reduction in dose;<br>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. |

## 15.2 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 |

## 15.3 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 15.2, above.

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:

CRO Medical Monitor:
Raphael Ryan Zantua, MD
Phone: +1 267 645 3494, +1 857 296 2093
e-mail: RaphaelRyan.Zantua@iconplc.com

Sponsor Medical Monitor:
Name: Mark L. Levitt, MD PhD
Phone: +972-(0)58-760-1010 (Israel), +1-914-294-3988 (US)
e-mail: mark@redhillbio.com

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.

## 15.4 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

## 15.5 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 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.

### 15.5.1 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, 2 weeks 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.

### 15.5.2 Adverse Events of Special Interest

The following adverse events are of special interest.

Patients who experience either of the following, at the discretion of the investigator, must be notified to the medical monitor immediately, 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

### 15.5.3 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.

### 15.5.4 Data Safety Monitoring Board

A data safety monitoring board (DSMB) will be convened for the safety oversight of the study. A DSMB charter will be provided as a separate document.

The DSMB meetings to review the safety data, will be planned after 30% and 60%, or when approximately 12 or 24 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 15.5.2), 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, as the sample size is not sufficient to determine futility conclusions.

# 16 ETHICS

## 16.1 Investigator Responsibilities

### 16.1.1 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.

### 16.1.2 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.

### 16.1.3 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.

### 16.1.4 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.

### 16.1.5 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.

### 16.1.6 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)

### 16.1.7 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.

### 16.1.8 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.

### 16.1.9 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.

### 16.1.10 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.

## 16.2 Sponsor Responsibilities

### 16.2.1 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.

### 16.2.2 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.

### 16.2.3 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.

### 16.2.4 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.

### 16.2.5 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.

### 16.2.6 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.

### 16.2.7 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.

# 17 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.

## 17.1 Sample Size Considerations

It is planned to enroll approximately 40 eligible patients into the double-blind treatment phase, to receive either opaganib added to standard of care (n=20), or matching placebo added to standard of care (n=20). The sample size for this Proof of Concept study was not chosen for statistical consideration, as there are no formal statistical inferences planned. The size of the study is judged adequate for the preliminary evaluation objectives.

## 17.2 Stratification

Patients will be stratified based on a minimization algorithm taking the following three parameters into account: age at screening, ≥70 years of age, (yes or no); HbA1c at screening, ≥6.5, (yes or no); oxygen requirement at baseline, requiring non-invasive positive pressure ventilation (e.g. via BIPAP, CPAP), (yes or no)

## 17.3 Analysis of the primary efficacy endpoint

The primary efficacy objective of the study is to evaluate the effect of Opaganib on total supplemental oxygen requirement (area under the curve) using daily oxygen flow (L/min) measurements for 14 days (Day 1 to Day 14). The primary efficacy endpoint will calculate for each patient the area under the curve of the supplemental oxygen requirement through day 14, 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. If several values of oxygen requirement (L/min) are recorded in a certain day, for the primary analysis the highest of these values will be taken. In the primary analysis, for patients who die before Day 14, or require intubation and mechanical ventilation, missing values will be assigned the maximal supplemental oxygen flow requirement of 8L/min. For patients discharged from hospital on supplemental oxygen prior to Day 14, if no values are collected by the site after discharge, the oxygen requirement (L/min) on the day of discharge will be assigned thereafter for each day to Day 14.

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,

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.

It is planned to collect supplemental oxygen requirement up to Day 14 even if a patient discontinues treatment prior to Day 14 but continues in the study to Day 14. Further, it is assumed that loss to follow up such that vital status up to Day 14 will be missing is unlikely. Therefore, the primary

analysis will assume that in case that all supplemental oxygen values are missing after treatment discontinuation, the individual AUC will be calculated where the last value is carried forward - until Day 14, or death, if occurred before. A sensitivity analysis to the above 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.

## 17.4 Safety Analyses

The safety and tolerability of opaganib will be determined by reported AEs, physical examinations, vital signs, and laboratory tests. Patients who receive at least one dose of study drug are considered evaluable for safety (Safety analysis set). Detailed specification of the safety analyses will be provided in the SAP.

# 18 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 2a Study, in Adult Subjects Hospitalized with 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 |

# 19 REFERENCES

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