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Opaganib in COVID-19 pneumonia: Results of a randomized, placebo-controlled Phase 2a trial

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- Methodology – Kevin L. Winthrop, Ofra Barnett-Griness, Gilead Raday, Gina Eagle, Vered Katz Ben-Yair, Mark L. Levitt
- Data curation – Ofra Barnett-Griness, Aida Bibliowicz, Gilead Raday, Gina Eagle, Vered Katz Ben-Yair, Mark L. Levitt, Reza Fathi, Patricia Anderson, Harold S. Minkowitz

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
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Investigators – Alan W. Skolnick, Adnan M. Rafiq, Scott H. Beegle, Julian Suszanski, Guenther Koehne, Michael S. Gordon

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Running title: Opaganib in COVID-19 pneumonia

10.14 Pneumonia: Viral Infections

Study impact: The findings of this study indicated symptomatic clinical improvement in patients with COVID-19 pneumonia who are hospitalized and require supplemental oxygen. By diminishing or eliminating these patients’ need for supplemental oxygen and shortening their time to hospital discharge, opaganib may offer a much needed treatment option for hospitalized patients, helping to speed their recovery and ease the burden on limited health resources.

Total word count: 2972 words
This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.
ABSTRACT

Rationale: Opaganib, an oral sphingosine kinase-2 inhibitor with antiviral and anti-inflammatory properties, was shown to inhibit SARS-CoV-2 replication in vitro. We thus considered that opaganib could be beneficial for moderate to severe COVID-19 pneumonia.

Objectives: To evaluate the effect of opaganib on supplemental oxygen requirements, time to hospital discharge and its safety in COVID-19 pneumonia hospitalized patients requiring supplemental oxygen.

Methods: This Phase 2a, randomized, double-blind, placebo-controlled study, was conducted between July and December 2020 in eight sites in the USA. Forty-two enrolled patients received opaganib (n=23) or placebo (n=19) added to standard of care for up to 14 days and were followed up for 28 days after their last dose of investigational product.

Main Results: By Day 14, 50.0% of patients in the opaganib and 22.2% in the placebo group no longer required supplemental oxygen for at least 24 hours, while 86.4% and 55.6%, respectively, were discharged from hospital. The relative decrease in total supplemental oxygen requirement from baseline to Day 14 was 61.6% in the opaganib versus 46.7% in the placebo arms. The incidence of ≥ Grade 3 treatment-emergent adverse events was 17.4% and 33.3% in the opaganib and placebo groups, respectively. Three deaths occurred in each group.

Conclusions: In this proof-of-concept study, patients receiving oral opaganib required less supplemental oxygen, resulting in earlier hospital discharge, with no safety concerns arising. These findings support further evaluation of opaganib in this population.

Clinical trial registered with www.clinicaltrials.gov (NCT 04414618).

Total word count: 233

Keywords: hospitalization, sphingosine-kinase-2, supplemental oxygen, SARS-CoV-2
INTRODUCTION

Acute pneumonia due to Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection leading to coronavirus disease 2019 (COVID-19) can be life-threatening. COVID-19 was first reported in China in December 2019 (1, 2), and was declared a global pandemic by the World Health Organization (WHO) in March 2020 (1, 2). Typical symptoms of SARS-CoV-2 infection include fever, fatigue, dry cough, shortness of breath, but can evolve to acute respiratory distress syndrome. Among patients with COVID-19, 80% present with symptoms of mild to moderate severity, with or without pneumonia, while 5-14% develop serious or critical respiratory disease, requiring intensive care unit support (1, 3, 4). The mortality rate of COVID-19 ranges from 0.1 to 19.7%, depending on several factors, such as country of origin, socioeconomic background, comorbidities such as diabetes and cardiovascular disease, and disease severity (5–9). These comorbidities and advanced age (especially > 65 years) increase the risk of mortality (10, 11).

Hospitalized COVID-19 patients often require supplemental oxygen to maintain adequate oxygenation (4, 10). Some pharmacological agents, including corticosteroids and remdesivir, have been widely used as standard of care (SoC) for these patients, with remdesivir first approved in the USA for emergency use in hospitalized patients in May 2020 (12).

Opaganib (RedHill Biopharma, Tel-Aviv, Israel) is a first-in-class orally available, small molecule, selective sphingosine kinase-2 (SK-2) inhibitor with antiviral and anti-inflammatory properties (13). Multiple ongoing clinical trials are evaluating the use of opaganib as therapy for cancer. The antiviral effect of opaganib was demonstrated in various preclinical studies. Reid and colleagues showed that a decreased expression or pharmacologic inhibition of SK-2 significantly inhibited Chikungunya virus replication (14).
Xia and et al., opaganib was shown to reduce fatality rates from influenza A viral infection in mice (15). Moreover, in a preliminary study using an in vitro model of human bronchial tissue, we recently demonstrated that opaganib has potent antiviral activity against SARS-CoV-2 (16). We hypothesized that the antiviral and anti-inflammatory effects of opaganib would be beneficial for the treatment of SARS-CoV-2 infection, particularly for patients with moderate to severe COVID-19 pneumonia requiring supplemental oxygen. In a small cohort of patients with severe COVID-19 pneumonia, where opaganib was offered through compassionate use, it appeared to improve clinical and laboratory parameters in treated patients, and was safe and well tolerated (17).

This Phase 2a proof-of-concept, placebo-controlled study was designed to evaluate the effect of opaganib when added to SoC in hospitalized patients with COVID-19 pneumonia who required supplemental oxygen. Efficacy endpoints evaluated the change in oxygen requirements, clinical improvement parameters, such as time to hospital discharge, as well as safety assessments.

**METHODS**

**Design**

This was a Phase 2a, proof-of-concept, multi-center, randomized, double-blind, parallel arm, placebo-controlled study conducted in eight sites in the USA. Eligible patients received opaganib or matching placebo twice daily added to SoC (per regional, institutional or physician practices). Eligible participants were adults aged 18-80 years inclusively, with SARS-CoV-2 infection determined by polymerase-chain-reaction (PCR) analysis in a
nasopharyngeal sample, and pneumonia determined by chest X-ray. The full list of eligibility
criteria is provided in the online data supplement (Section-1).

**Intervention**

Participants were randomized 1:1 to receive 2 x 250 mg opaganib oral capsules or matching
placebo every 12 hours for up to 14 days (Days 1-14). This dose had been determined in a
Phase 1 clinical study in oncology patients as the maximum safe and tolerable dose (18).
Patients discharged prior to/at Day 10 completed only ten days of treatment. After their last
study drug dose, participants were followed for up to 28 days (safety follow-up). Treatment
assignments remained blinded to the patients, investigators, hospital staff, and sponsor
(RedHill Biopharma).

**Outcomes**

Given the exploratory nature of this proof-of-concept study, we sought to evaluate a number
of clinically meaningful outcomes. We designated a primary outcome measure a priori with
regard to measuring total supplemental oxygen requirements from baseline to day 14 (area-
under-the-curve [AUC]) using daily oxygen flow measurements. Primary endpoint details are
provided in the online data supplement (Section-2), together with a complete list of
secondary, post-hoc, safety and exploratory endpoints. Presented herein are the following
clinically meaningful secondary outcomes: (a) time to 50% reduction from baseline in
supplemental oxygen requirement by Day 14, (b) percentage of patients no longer receiving
supplemental oxygen for at least 24 hours by Day 14, (c) time to intubation and mechanical
ventilation by Day 14, (d) mortality by Day 30; post-hoc outcomes: (a) percentage of patients
no longer receiving supplemental oxygen for at least 24 hours by Day 14 per SoC regimen,
(b) time to intubation and mechanical ventilation by safety follow-up, (c) mortality by safety
follow-up, (d) incidence of hospital discharge by Day 14 and by safety follow-up, (e) time to 
≥2 points improvement in the WHO Ordinal Scale (19) by Day 14; safety outcome: incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs.

Statistics

As the sample size (~40 patients) was not chosen for statistical consideration, efficacy interpretation is based on numerical comparisons of descriptive statistics. Statistical methodology details are provided in the online data supplement (Section-3). Baseline characteristics are presented for the Intent-to-Treat (ITT) population (all randomized patients). Efficacy endpoints were analyzed for the modified ITT (mITT) population (patients who took at least one dose of study drug). Safety evaluations were performed for the safety population (patients who took at least one dose of study drug).

RESULTS

A diagram of the study flow is presented in Figure 1. The ITT population comprised of 42 eligible patients, enrolled from July to November 2020. Of these, 23 patients were randomized to receive opaganib and 19 patients were randomized to receive placebo (randomization details are provided in the online data supplement, Section-4). One patient in each group did not receive study drug and was excluded from the safety and mITT populations. One patient, randomized to placebo, was mistakenly given opaganib on Day 10 and Day 11.
Demographic and other baseline characteristics

The main demographic and baseline characteristics of patients in the ITT population are presented in Table 1. Most patients were male (64.3%) with an overall patient median age of 58.0 years. The mean time from diagnosis to hospitalization was 2.5 days (median 0.0 days) and the mean time from diagnosis to randomization was 6.2 days (median 4.0 days), and similar for both groups (Table 1).

Remdesivir and/or high dose corticosteroids (dexamethasone, prednisone, and methylprednisolone) comprised known effective SoC for COVID-19 and were co-administered with opaganib in 22 (95.7%) patients and with placebo in all 18 (100%) patients. This included remdesivir in 10 (43.5%) patients in the opaganib and nine (50.0%) in the placebo group, and high dose corticosteroids in 21 (91.3%) and all 18 (100%) patients, respectively.

Treatment compliance

Compliance was assessed in a subset of the safety population comprising of 21 patients of the opaganib and 18 patients of the placebo group (further details are provided in the online data supplement – Section-5). For two patients in the opaganib arm, compliance was not defined: for the patient randomized to placebo who took opaganib on one day, the expected number of opaganib doses was zero; for the other patient compliance could not be assessed as he was lost to follow-up. The mean (±standard deviation) compliance was 90.05% (±21.523) in the opaganib and 98.41% (±3.917) in the placebo groups, respectively.

Requirement of supplemental oxygen by Day 14
The Kaplan-Meier analysis for no longer requiring supplemental oxygen for at least 24 hours by Day 14 showed a higher estimated cumulative incidence in patients on opaganib (50%) compared to patients on placebo (22.2%) (Figure 2 and Table 2).

The sub-group analysis based on SoC regimen, showed consistent findings across all SoC sub-groups (Table 2). Specifically, the estimated cumulative incidence of no longer receiving supplemental oxygen by Day 14 in patients receiving opaganib on top of remdesivir in combination with high dose corticosteroids (44.4%), and in those receiving opaganib on top of high dose corticosteroids only (54.6%), was consistent with that observed in the overall opaganib group, and higher than in the respective subgroups receiving placebo on top of the SoC (44.4% versus 22.2% and 54.6% versus 22.2%, respectively).

The median Kaplan-Meier estimated time to 50% reduction from baseline in supplemental oxygen requirement based on oxygen flow (L/min) between Day 1 and Day 14 was 5 days in the opaganib versus 8 days in the placebo group. The Kaplan-Meier estimated cumulative incidence of this event by Day 14 was 81% in the opaganib group compared to 66.7% in the placebo group.

**Intubation and mechanical ventilation, and mortality during the course of the study and at the end of follow-up**

The Kaplan-Meier estimated cumulative incidence of intubation and mechanical ventilation at Day 14 was 9.6% in the opaganib group and 11.1% in placebo. There were two intubation and mechanical ventilation events in each treatment group. There were no subsequent intubations and mechanical ventilations through the end of safety follow-up.
Regarding mortality, a total of three patients in the opaganib group and two patients in the placebo group died by Day 30. The Kaplan-Meier estimated cumulative incidence of death by Day 30 was 15.0% in the opaganib and 11.9% in the placebo group. An additional death occurred in the placebo group by the end of safety follow-up. The Kaplan-Meier estimated cumulative incidence of death by the safety follow-up was 15.0% in the opaganib group and 19.2% in the placebo group.

**Hospital discharge**

The Kaplan-Meier estimated cumulative incidence of hospital discharge by Day 7 was 68.2% in the opaganib and 50.0% in the placebo groups, and 86.4% versus 55.6%, by Day 14, respectively, (Figure 3).

In a related post-hoc analysis, we derived the time to a two point improvement in the WHO Ordinal Scale (19) (details of the scale are provided in the online data supplement, Table E1). All patients, except for one who did not require supplemental oxygen at baseline, started the treatment while hospitalized and receiving supplemental oxygen (WHO ordinal score of 4 or 5). Patients discharged from hospital had to reach a score of at most 2, i.e., show improvement of at least two points on the WHO ordinal score. The Kaplan-Meier estimated cumulative incidence of at least a two point improvement on the WHO Ordinal Scale by Day 14 was 81.8% in the opaganib group, and 55.6% in the placebo group (Table 3). Additionally, the opaganib group had a shorter estimated median time to achieving this improvement compared to placebo (6.0 and 7.5 days, respectively).
Total supplemental oxygen requirement using the maximal daily oxygen flow over 14 days

The relative benefit derived for each group was calculated as 61.6% (-770/-1250) for opaganib (n=21) and 46.7% (-583.6/-1250) for placebo (n=18) (Figure 4; more information on the calculation of the relative benefit in each group is provided in the online data supplement, Section-2). This was a post-hoc analysis to the pre-defined primary endpoint; as more information on the course of COVID-19 pneumonia became available, these endpoints, quantifying total supplemental oxygen required over time (across various devices), proved to be of less clinical value than originally assessed.

Safety evaluation – treatment emergent adverse events

The incidence of TEAEs was similar between treatment groups (52.2%, in the opaganib group versus 50.0% in the placebo group; Table 4). Generally, each unique TEAE term was reported singly by one patient (either in the opaganib or placebo group). The only TEAEs reported by two patients (8.7% in the opaganib group), and with a higher incidence in the opaganib group than in placebo, were hypokalemia (reported in one patient on placebo) and diarrhea (reported in no patients on placebo).

Serious TEAEs were reported in 13.0% of the patients in the opaganib group and 27.8% of those in the placebo group. TEAEs of Grade 3 and above were reported in 17.4% of the patients in the opaganib group and 33.3% of the patients in the placebo group, with no TEAEs of Grade 3 and above reported at a higher frequency in the opaganib group compared to placebo (Table 4). There were no reported TEAEs resulting in dose reductions. TEAEs
leading to treatment withdrawal were reported in 17.4% of the patients in the opaganib group, and 5.6% of the patients in the placebo group. Three death cases were reported in each group.

**DISCUSSION**

This proof-of-concept study explored the effectiveness and safety of oral opaganib in hospitalized patients with COVID-19 pneumonia requiring supplemental oxygen. Results demonstrated clinical improvement as measured by reduced need for supplemental oxygen, improved WHO level in the scale for clinical improvement and in time to discharge. The safety profile of opaganib was not materially different than that of placebo.

Several lines of preliminary evidence suggested that opaganib may be particularly relevant to COVID-19. Prior to the onset of the COVID-19 pandemic, opaganib had demonstrated antiviral and anti-inflammatory effects in several preclinical models, including amelioration of *Pseudomonas aeruginosa*-induced lung injury and reduction of fatality rates from influenza virus infection (20, 21); inhibition of host inflammatory responses in several disease models (22, 23); and exertion of various effects on the immune system (24). Since then, opaganib has been shown to have potent antiviral activity against SARS-CoV-2 in a preclinical study using an *in vitro* model of human bronchial tissue (16) and to be beneficial when offered through compassionate use to patients with moderate to severe COVID-19 pneumonia requiring supplemental oxygen via high-flow nasal cannulae (17). As opaganib targets a host cell factor rather than the virus directly, development of resistance is less likely. This is of particular interest in SARS-CoV-2 infection, given its rapidly emerging mutations and different viral strains.
The antiviral agent, remdesivir, has been approved for treatment in certain stages of COVID-19; however, it is administered intravenously and lacks anti-inflammatory properties (6). In contrast, opaganib is an oral agent with both antiviral and anti-inflammatory properties. Moreover, opaganib is stable at room temperature for several years (RedHill Biopharma Ltd., unpublished data). These factors support opaganib as a much needed, practical and convenient potential treatment of COVID-19 pneumonia.

The current study was designed to primarily assess the change in total supplemental oxygen requirements per patient during the 14-day course of treatment. The prespecified analyses used absolute change and a post-hoc analysis utilized percent change. This post-hoc analysis demonstrated an apparent difference, with the total supplemental oxygen requirement for patients on opaganib being less than those on placebo. However, as the pandemic progressed, with more information on the course of COVID-19 pneumonia becoming available, it became evident that the clinical interpretation of this endpoint was limited given high variability in baseline values and in the devices used to deliver oxygen. Additionally, since most patients were discharged before Day 14, some of the predefined secondary efficacy analyses (based on 14 days of in-patient data collection) could not be performed. In fact, as a higher proportion of patients on opaganib were discharged from the hospital before Day 14 compared to those on placebo, missing data is not balanced, and likely to introduce a bias to these secondary efficacy analyses. Thus, we were unable to assess several of our prespecified secondary endpoints due to missing data. As improvement in supplemental oxygen requirement had become a commonly used criterion for hospital discharge in COVID-19 patients (25), our pre-defined secondary analysis of no longer requiring supplemental oxygen for at least 24 hours was the most clinically relevant endpoint. Further post-hoc analyses demonstrated that compared to placebo, 1) the benefit of no longer requiring supplemental
oxygen at Day 14 when treated with opaganib was maintained irrespective of the background SoC; 2) hospital discharge was more rapid for patients on opaganib; and 3) a derived 2-point improvement in the WHO Ordinal Scale occurred sooner for patients in the opaganib group. These post-hoc analyses were highly indicative of clinical improvement in disease severity, supporting the pre-specified efficacy endpoints. All evaluated secondary and post-hoc efficacy endpoints demonstrated a numerically superior benefit for patients on opaganib compared with those on placebo.

Opaganib was shown to be well-tolerated in patients with COVID-19 pneumonia, with no new safety signals emerging. The only TEAE of Grade 3 and above reported at a higher frequency in the opaganib group than placebo was a Grade 3 rash in a single patient, that resolved with stopping study drug. Rash is a known uncommon toxicity of opaganib. Three patients in the opaganib group and five patients on placebo experienced serious TEAEs. TEAEs leading to treatment withdrawal were reported in 17.4% of the patients on opaganib, and 5.6% of the patients on placebo. By the safety follow-up timepoint, there were three deaths recorded in each group, none deemed treatment related. The overall incidence of TEAEs and TESAEs were similar in both treatment groups.

Limitations
The main limitation of this study is its small sample size, allowing for descriptive analyses rather than meaningful statistical interpretation. A further limitation was the imbalance in supplemental oxygen requirement at baseline, a result of the small sample size despite randomization. Nonetheless, the results suggest a potential clinical benefit for opaganib compared to placebo. An additional limitation of the study is that certain pre-defined secondary endpoints that relied on inpatient data collection could not be assessed. This was
due to changing standard of practice leading to earlier discharge of patients than was anticipated at the time of protocol development. Notably, a greater proportion of patients on opaganib versus placebo were discharged prior to Day 14. Lastly, the clinical interpretation of the primary endpoint was limited, as described above, leading to the addition of post-hoc analyses to help with the overall interpretation of the data.

Conclusions

Taken together, the results of this Phase 2a study demonstrate the potential benefit of opaganib across various clinically meaningful outcome measures in patients with COVID-19 pneumonia, with no new safety concerns. Based on these findings, further evaluation of opaganib is currently ongoing in larger randomized studies as a potential treatment for moderate-severe COVID-19 pneumonia in hospitalized patients requiring supplemental oxygen, with a global Phase 2/3 (NCT04467840) having already completed enrollment (16).

AUTHOR DISCLOSURES are available with the text of this article at www.atsjournals.org.
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REFERENCES:


19. WHO R&D Blueprint. COVID-19 Therapeutic Trial Synopsis. 2020;


FIGURES LEGENDS

**Figure 1.** Study flow diagram. Abbreviations: ITT – Intent-to-Treat population; mITT – modified Intent-to-Treat population.

**Figure 2:** Kaplan-Meier curve of time (days) to no longer receiving supplemental oxygen for at least 24 hours by Day 14 (mITT population). Death was censored at Day 14 as the worst outcome for this endpoint.

**Figure 3:** Kaplan-Meier curve of time to hospital discharge by Day 14 in the opaganib and placebo groups (mITT population). Death was censored at Day 14 as the worst outcome for this endpoint.

**Figure 4:** Dot plot of relative improvement in total supplemental oxygen from Day 1 to Day 14 of treatment in the opaganib and placebo groups in the mITT population. The total number of patients in the opaganib group is 21 (rather than 22 in the modified Intent-to-Treat [mITT] population) because one patient did not require oxygen at baseline and was therefore excluded from this analysis.
FIGURES

Figure 1

- Assessed for eligibility (n=49)
  - Excluded (n=7)
    - Not meeting all inclusion/exclusion criteria (n=7)

  - Randomized (n=42)

  - Allocation
    - Allocated to opaganib (n=23)
      - Received opaganib (n=22)
      - Not treated (n=1)
    - Allocated to placebo (n=19)
      - Received placebo (n=18)
      - Not treated (n=1)

  - Follow-up
    - Early study termination (n=8)
      - Death (n=3)
      - Withdrawal of consent (n=2)
      - Lost to follow-up (n=2)
      - Investigator's decision (n=1)
    - Premature treatment discontinuation (n=3)
      - Adverse Event (n=2)
      - Withdrawal of consent (n=1)
    - Early study termination (n=7)
      - Death (n=3)
      - Withdrawal of consent (n=1)
      - Lost to follow-up (n=3)
    - Premature treatment discontinuation (n=2)
      - Adverse Event (n=1)
      - Other (n=1)

  - Analysis
    - ITT (n=23)
    - Safety population (n=23)\(^1\)
    - mITT population (n=22)
    - ITT (n=19)
    - Safety population (n=18)\(^1\)
    - mITT population (n=18)

\(^1\) One patient in each group was not treated and excluded from the safety population. One patient randomized to placebo who was mistakenly given opaganib on Day 10 and Day 11 has been included in the safety population of both the opaganib and the placebo groups.
Figure 4
**TABLES**

**Table 1:** Main patient demographic and baseline characteristics in the opaganib and placebo groups and overall.

<table>
<thead>
<tr>
<th>Parameter (ITT population)</th>
<th>Opaganib (N=23)</th>
<th>Placebo (N=19)</th>
<th>Overall (N=42)</th>
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<td>0.0 (-5, 20)</td>
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<tr>
<td>Time from diagnosis to randomization (days), median (range)</td>
<td>4.0 (1, 33)</td>
<td>4.0 (2, 18)</td>
<td>4.0 (1, 33)</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c – hemoglobin A1c

* Two patients in each group had missing information on weight at baseline, resulting in n=21 patients in the opaganib group and n=17 patients in the placebo group.

† One patient in the placebo group had missing information on symptoms onset, resulting in n=18 patients in the placebo group.
Table 2: Kaplan-Meier estimate of the cumulative incidence of no longer receiving supplemental oxygen for at least 24 hours by Day 14 per standard of care regimen of interest in the opaganib and placebo groups. Death was censored at 14 Days.

<table>
<thead>
<tr>
<th>Standard of Care Regimen Group (mITT population)*</th>
<th>Opaganib (N=22)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (N)</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Number of events†, n (%)</td>
<td>11 (50.0)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Cumulative incidence at Day 14^</td>
<td>50.00</td>
<td>22.22</td>
</tr>
<tr>
<td>Treated with combination of remdesivir and high dose corticosteroids (N)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Number of events†, n (%)</td>
<td>4 (44.4)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Cumulative incidence at Day 14^</td>
<td>44.44</td>
<td>22.22</td>
</tr>
<tr>
<td>Treated only with remdesivir (N)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Number of events†, n (%)</td>
<td>1 -</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative incidence at Day 14^</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>Treated only with high dose corticosteroids (N)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Number of events†, n (%)</td>
<td>6 (54.5)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Cumulative incidence at Day 14^</td>
<td>54.55</td>
<td>22.22</td>
</tr>
<tr>
<td>Neither Standard of Care (N)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Number of events†, n (%)</td>
<td>1 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative incidence at Day 14^</td>
<td>100.00</td>
<td>-</td>
</tr>
</tbody>
</table>

* The number of patients treated with specific standard of care regimen is presented.
† Event is defined as no longer receiving supplemental oxygen for at least 24 hours.
^ The cumulative incidence of patients was estimated with the Kaplan–Meier method.

Table 3: Time to two point improvement on the WHO Ordinal Scale by Day 14 (mITT population).

<table>
<thead>
<tr>
<th>mITT population</th>
<th>Opaganib (N=22)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with two-point improvement by Day 14 (%)</td>
<td>18 (81.8)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Number of censored by Day 14 (%)</td>
<td>4 (18.2)</td>
<td>8 (44.4)</td>
</tr>
<tr>
<td>Kaplan-Meier cumulative incidence* (95% CI)</td>
<td>81.82 (63.71 - 94.32)</td>
<td>55.56 (34.88 - 78.42)</td>
</tr>
<tr>
<td>Kaplan-Meier median estimate (95% CI) (days)</td>
<td>6.00 (4.00 – 14.00)</td>
<td>7.50 (4.00 – NA*)</td>
</tr>
</tbody>
</table>

Abbreviations: CI – Confidence interval; NA – Not achieved
* The cumulative incidence of patients was estimated with the Kaplan–Meier method.
Table 4: Treatment emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term in the opaganib and placebo groups (safety population)

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Opaganib (N=23)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>12 (52.2)</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>Any TEAE Grade 3 and above</td>
<td>4 (17.4)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Any Serious TEAE</td>
<td>3 (13.0)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Any treatment-related TEAE</td>
<td>2 (8.7)</td>
<td>-</td>
</tr>
<tr>
<td>Any treatment-related Grade 3 and above TEAE</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>Any treatment-related serious TEAE</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TEAEs Grade 3 and above by MedDRA Preferred Term

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Opaganib (N=23)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>1 (4.3)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>COVID-19 pneumonia</td>
<td>1 (4.3)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>Septic shock</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Fibrin D dimer increased</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>Troponin I increased</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>White blood cell count increased</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Glucose tolerance impaired</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1 (4.3)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (8.7)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Pneumonia aspiration</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>Shock</td>
<td>-</td>
<td>1 (5.6)</td>
</tr>
</tbody>
</table>