Press Release

RedHill Biopharma Reports Further Analysis of Phase 2/3 Data Including a 62% Reduction in Mortality with Oral Opaganib in Moderately Severe COVID-19 Patients

62% statistically significant reduction in mortality shown for moderately severe COVID-19 patients group treated with opaganib vs. the placebo-controlled arm (7 deaths in the 117-patient opaganib arm vs. 21 deaths in the 134-patient placebo arm; nominal p-value=0.019)

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21% statistically significant efficacy benefit with opaganib in reaching room air by Day 14, the study primary endpoint (77% of opaganib patients vs 63.5% on placebo; nominal p-value=0.033)

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A median four days earlier hospital discharge for opaganib-treated patients vs. placebo (10 days for opaganib arm vs. 14 days for placebo) a cumulative saving of 524 days of hospitalization across the group by Day 42 (nominal p-value=0.0195)

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The moderately severe group comprised 53% of study participants requiring a Fraction of inspired Oxygen (FiO2) up to 60% at baseline (inhaled supplemental oxygen via nasal cannula or face mask)

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Data indicates a potential meaningful benefit with opaganib for these hospitalized, moderately severe COVID-19 patients - a group at high risk of disease progression, morbidity and mortality; the data also supports opaganib's potential use in earlier stages of COVID-19 disease, consistent with opaganib's U.S Phase 2 study results and the demonstrated potent antiviral inhibition of SARS-CoV-2 variants

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RedHill will hold a webcast on Thursday, October 7, 2021, at 08:30 am EDT to further discuss these additional analyses

TEL AVIV, Israel and RALEIGH, NC, October 4, 2021, RedHill Biopharma Ltd. (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today reported new data from the opaganib global Phase 2/3 study in hospitalized patients with severe COVID-19 pneumonia showing that treatment with oral opaganib (ABC294640)[1] vs. the placebo-controlled arm resulted in a 62% statistically significant reduction in mortality as well as statistically significant improved outcomes in time to room air and median time to hospital discharge in a group of 251 hospitalized, moderately severe COVID-19 patients, comprising 53% of the 475 study participants.

These important new results are from a post-hoc analysis of data from the 251 study participants requiring a Fraction of inspired Oxygen (FiO2) up to 60% at baseline. Patients with FiO2 ≤ 60% are still considered to be severely affected and typically require oxygen supplementation via a nasal cannula or face mask.

"These new findings support the potential for opaganib's use in hospitalized, moderately severe COVID-19 patients - a key group of patients that are at high risk of disease progression, morbidity and mortality, and who may benefit from opaganib's combined antiviral and anti-inflammatory activities," **said Mark L. Levitt, MD, Ph.D., Medical Director at RedHill**. "The results provide a strong rationale for opaganib's potential efficacy in hospitalized patients in need of oxygen supplementation up to 60% FiO2, a large proportion of hospitalized COVID-19 patients. The Phase 2/3 study results are also consistent with opaganib's earlier U.S Phase 2 study results and the demonstrated potent antiviral inhibition of SARS-CoV-2 variants in human bronchial epithelial cells, providing further support for its potential in earlier stages of disease where viral load is higher."

"We are excited about this promising and robust dataset. We are not aware of any other novel oral pill-based therapy that has shown a similar magnitude of difference in the mortality outcomes of hospitalized patients who are at this moderately severe stage of disease. The data indicates opaganib's potential to provide an effective option, in an easy to take and distribute pill-form, to help prevent patient deterioration and mortality," **said Dror Ben-Asher, RedHill's CEO**. "Pinpointing the most relevant target patient population is particularly challenging with novel drugs, novel mechanisms of action and a previously unknown disease. This trial and these data have given us a clear indication of which groups of patients are likely to benefit the most from opaganib."

Analyses of the FiO2 up to 60% patient subset from the opaganib Phase 2/3 study (n=251), the approximate median for FiO2 levels in the study, who were treated with either opaganib or placebo in addition to standard-of-care (including dexamethasone and/or remdesivir) demonstrate consistent benefit across endpoints, in this subset of hospitalized moderately severe patients. Given the post-hoc characteristics of this subset, statistical inferences of significance cannot be formally attributed (nominal values presented). The Company also conducted a Sensitivity Analysis to account for missing data interpretability[2]:

- **Mortality**: Opaganib treatment resulted in a statistically significant 62% reduction in mortality (7/117 patients treated with opaganib vs. 21/134 for placebo; nominal p-value=0.019, Relative Risk 2.6) (Sensitivity Analysis: 5/117 vs. 16/134, 64% efficacy benefit; nominal p-value=0.033, Relative Risk - 2.8).

  A detailed analysis of baseline risk factors and their potential impact on the mortality outcome in the sensitivity analysis group has also been undertaken, showing that the benefit is robustly maintained irrespective of the subgroups/risk factors, confirming that the positive outcome observed is due to opaganib.

- **Reaching Room Air by Day 14 (primary endpoint of the study):** 77% of opaganib-treated patients reached room air by Day 14 vs. 63.5% for placebo – an efficacy benefit of 21% with opaganib (nominal p-value= 0.033).

- **Median time to discharge:** Patients treated with opaganib showed median time of 10 days to discharge vs. 14 days for the placebo arm, resulting in a saving of four days hospitalization per opaganib patient and saving a total of 524 cumulative days of hospitalization across the group by Day 42, nominal p-value=0.0195

- **Safety**: Overall adverse events were balanced between the opaganib and placebo groups, suggesting good safety, with no new safety signals emerging, further supporting potential use in this patient population and earlier stage populations. [3]

The multi-center, randomized, double-blind, parallel-arm, placebo-controlled global Phase 2/3 study enrolled 475 subjects with severe COVID-19 pneumonia requiring hospitalization and treatment with supplemental oxygen. Subjects were randomized at a 1:1 ratio to receive either opaganib or placebo, on top of standard-of-care therapy.

The new data of the sub-group analysis follows the Company's previously announced top-line results of the Phase 2/3 study. Analysis of the top-line data is still ongoing, including further analysis of the potential for increased benefit of treatment with opaganib in patients at earlier stages of disease. RedHill intends to discuss the study outcomes with regulators, including U.S. FDA and U.S. government agencies, as well as other regulators and governments and international agencies, to help determine next steps.

Opaganib is a novel small molecule investigational drug in oral pill form. Opaganib has a unique dual antiviral and anti-inflammatory mechanism of action that acts on the viral cause and inflammatory effect of COVID-19. It is believed to exert its antiviral effect by selectively inhibiting SK2, a key enzyme produced in human cells that may be recruited by the virus to support its replication and is expected to be effective against emerging viral variants, having already preclinically demonstrated strong inhibition against variants of concern, including *Delta*.

Webcast and Conference Call Information:

The Company will host a webcast on Thursday, October 7, 2021, at 8:30 a.m. EDT, during which it will present the additional analysis of the Phase 2/3 study results and answer questions.

The webcast including slides will be broadcast live on the Company's website, https://www.redhillbio.com/investors/events-and-presentations/default.aspx, and will be available for replay for 30 days.

To participate in the conference call, please dial one of the following numbers 15 minutes prior to the start of the call: United States: +1-877-870-9135; International: +1 646-741-3167
and Israel: +972-3-530-8845; the access code for the call is: 4785122.

About Opaganib (ABC294640)
Opaganib, a new chemical entity, is a proprietary, first-in-class, orally-administered, sphingosine kinase-2 (SK2) selective inhibitor, with dual anti-inflammatory and antiviral activity. Opaganib is host-targeted and is expected to be effective against emerging viral variants, having already demonstrated strong inhibition against variants of concern, including *Delta*. Opaganib has also shown anticancer activity and positive preclinical results in renal fibrosis, and also has the potential to target multiple oncology, viral, inflammatory, and gastrointestinal indications.

Opaganib previously delivered positive U.S. Phase 2 data in patients with severe COVID-19, submitted for peer review and recently published in medRxiv.

Opaganib has also received Orphan Drug designation from the U.S. FDA for the treatment of cholangiocarcinoma and is being evaluated in a Phase 2a study in advanced cholangiocarcinoma and in a Phase 2 study in prostate cancer. Based on a preliminary review of partial unaudited data, the ongoing study in prostate cancer has met its primary endpoint. Patient accrual, treatment and analysis in this study are ongoing.

Opaganib demonstrated potent antiviral activity against SARS-CoV-2, the virus that causes COVID-19, inhibiting viral replication of all SARS-CoV-2 variants tested to date in an *in vitro* model of human lung bronchial tissue. Additionally, preclinical *in vivo* studies have demonstrated opaganib's potential to ameliorate inflammatory lung disorders, such as pneumonia, have demonstrated opaganib's potential to decrease renal fibrosis and have shown decreased fatality rates from influenza virus infection and amelioration of *Pseudomonas aeruginosa*-induced lung injury by reducing the levels of IL-6 and TNF-alpha in bronchoalveolar lavage fluids[4].

The ongoing clinical studies with opaganib are registered on www.ClinicalTrials.gov, a web-based service by the U.S. National Institute of Health, which provides public access to information on publicly and privately supported clinical studies.

The top-line results from the Company's Phase 2/3 study with opaganib are preliminary in nature. The Company intends to further examine the data from this study in greater detail, along with all the information gathered during this study, including all safety, and secondary outcome measures. Such analysis may result in findings which are new or inconsistent with the top-line data disclosed in this release. As such, investors should not rely on the analyses reported in this release as the final definitive results of the study.

About RedHill Biopharma

RedHill Biopharma Ltd. (Nasdaq: RDHL) is a specialty biopharmaceutical company primarily focused on gastrointestinal and infectious diseases. RedHill promotes the gastrointestinal drugs, **Movantik®** for opioid-induced constipation in adults[5], **Talicia®** for the treatment of *Helicobacter pylori (H. pylori)* infection in adults[6], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[7]. RedHill's key clinical late-stage development programs include: (i) **RHB-204**, with an ongoing Phase 3 study for pulmonary nontuberculous mycobacteria (NTM) disease; (ii) **opaganib (ABC294640)**, a first-in-class oral SK2 selective inhibitor targeting multiple indications with a Phase 2/3 program for COVID-19 and Phase 2 studies for prostate cancer and cholangiocarcinoma ongoing; (iii) **RHB-107** (**upamostat**), an oral serine protease inhibitor in a U.S. Phase 2/3 study as treatment for symptomatic COVID-19, and targeting multiple other cancer and inflammatory gastrointestinal diseases; (iv) **RHB-104**, with positive results from a first Phase 3 study for Crohn's disease; (v) **RHB-102** , with positive results from a Phase 3 study for acute gastroenteritis and gastritis and positive results from a Phase 2 study for IBS-D; and (vi) **RHB-106**, an encapsulated bowel preparation. More information about the Company is available at www.redhillbio.com / https://twitter.com/RedHillBio.

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements may be preceded by the words "intends," "may," "will," "plans," "expects," "anticipates," "projects," "predicts," "estimates," "aims," "believes," "hopes," "potential" or similar words. Forward-looking statements are based on certain assumptions and are subject to various known and unknown risks and uncertainties, many of which are beyond the Company's control and cannot be predicted or quantified, and consequently, actual results may differ materially from those expressed or implied by such forward-looking statements. Such risks and uncertainties include the risk that further analysis of the top-line results of the Phase 2/3 COVID-19 study for opaganib results in findings inconsistent with the data disclosed in this release; that no further COVID-19 studies for opaganib will be commenced, and if commenced, may not be successful, including with respect to moderately severe COVID-19 and patients in earlier stages of COVID-19 on low flow oxygen support; that any additional studies for opaganib in COVID-19 patients, even if successful, will not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib and RHB-107 will be required by regulatory authorities to support such potential applications and the use or marketing of opaganib or RHB-107 for COVID-19 patients, that opaganib and RHB-107 will not be effective against emerging viral variants, as well as risks and uncertainties associated with (i) the initiation, timing, progress and results of the Company's research, manufacturing, preclinical studies, clinical trials, and other

therapeutic candidate development efforts, and the timing of the commercial launch of its commercial products and ones it may acquire or develop in the future; (ii) the Company's ability to advance its therapeutic candidates into clinical trials or to successfully complete its preclinical studies or clinical trials (iii) the extent and number and type of additional studies that the Company may be required to conduct and the Company's receipt of regulatory approvals for its therapeutic candidates, and the timing of other regulatory filings, approvals and feedback; (iv) the manufacturing, clinical development, commercialization, and market acceptance of the Company's therapeutic candidates and Talicia®; (v) the Company's ability to successfully commercialize and promote Movantik®, Talicia® and Aemcolo®; (vi) the Company's ability to establish and maintain corporate collaborations; (vii) the Company's ability to acquire products approved for marketing in the U.S. that achieve commercial success and build and sustain its own marketing and commercialization capabilities; (viii) the interpretation of the properties and characteristics of the Company's therapeutic candidates and the results obtained with its therapeutic candidates in research, preclinical studies or clinical trials; (ix) the implementation of the Company's business model, strategic plans for its business and therapeutic candidates; (x) the scope of protection the Company is able to establish and maintain for intellectual property rights covering its therapeutic candidates and commercial products and its ability to operate its business without infringing the intellectual property rights of others; (xi) parties from whom the Company licenses its intellectual property defaulting in their obligations to the Company; (xii) estimates of the Company's expenses, future revenues, capital requirements and needs for additional financing; (xiii) the effect of patients suffering adverse events using investigative drugs under the Company's Expanded Access Program; and (xiv) competition from other companies and technologies within the Company's industry. More detailed information about the Company and the risk factors that may affect the realization of forward-looking statements is set forth in the Company's filings with the Securities and Exchange Commission (SEC), including the Company's Annual Report on Form 20-F filed with the SEC on March 18, 2021. All forward-looking statements included in this press release are made only as of the date of this press release. The Company assumes no obligation to update any written or oral forward-looking statement, whether as a result of new information, future events or otherwise unless required by law.

Company contact:
Adi Frish
Chief Corporate & Business Development Officer
RedHill Biopharma
+972-54-6543-112
adi@redhillbio.com

Media contacts:
U.S.: Bryan Gibbs, Finn Partners
+1 212 529 2236
bryan.gibbs@finnpartners.com
UK: Amber Fennell, Consilium
+44 (0) 7739 658 783
fennell@consilium-comms.com

[1] Opaganib is an investigational new drug, not available for commercial distribution.
[2] While the overall risk factors are balanced, we are evaluating each individually for potential effects on endpoints.
[3] A detailed safety analysis is still ongoing.
[4] Xia C. et al. Transient inhibition of sphingosine kinases confers protection to influenza A virus infected mice. Antiviral Res. 2018 Oct; 158:171-177. Ebenezer DL et al. Pseudomonas aeruginosa stimulates nuclear sphingosine-1-phosphate generation and epigenetic regulation of lung inflammatory injury. Thorax. 2019 Jun;74(6):579-591.
[5] Full prescribing information for Movantik® (naloxegol) is available at: www.Movantik.com.
[6] Full prescribing information for Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is available at: www.Talicia.com.
[7] Full prescribing information for Aemcolo® (rifamycin) is available at: www.Aemcolo.com.