NEWS RELEASE

RedHill Accelerates Opaganib's Nuclear Radiation Protection Program - Positive Data Published

11/14/2022

Strong preclinical data, recently published in the International Journal of Molecular Sciences, from eight U.S government-funded in-vivo opaganib studies, supports opaganib's potential as a nuclear radiation injury therapeutic for homeland security material threat medical countermeasures (MCM) and for antitumor radiotherapy

As an oral, small molecule pill that is highly stable with a more than five-year shelf-life, opaganib is easy to administer and distribute, supporting, if approved, potential central stockpiling by governments for possible use in mass casualty nuclear radiation incidents

Unlike current approved options such as iodine pills, opaganib's suggested protective effect in radiation injury is not thought to be limited to specific radioactive materials or individual parts of the body. Rather, opaganib's mechanism of action is believed to suppress ionizing radiation toxicity and inflammatory damage to normal tissue, and promote the robustness of hematopoietic stem cells from radiation damage, potentially supporting increased survival and decreased morbidity

Observations from multiple GI-focused in-vivo models indicate that opaganib may protect normal tissue from damage due to ionizing radiation exposure or cancer radiotherapy , improve antitumor activity and response to chemoradiation and enhance tolerability and survival

Independent external in-vivo studies of the radioprotective capacity of opaganib in bone marrow also show

enhanced survival against both lethal and half-lethal whole-body irradiation

Another study has been initiated recently, by RedHill and its partner Apogee Biotechnology Corporation, to assess protective effects of opaganib against radiation-induced hematologic and renal toxicity

Based on FDA guidance specific to opaganib, and subject to a recently scheduled follow-on meeting with FDA, RedHill expects development of opaganib as a homeland security nuclear medical countermeasure to follow the Animal Rule, under which pivotal animal model efficacy studies are applicable when human clinical trials are not ethical or feasible ; Discussions regarding further support, funding and development pathway to approval have been initiated with US and other governments

Sponsors of approved medical countermeasures product applications are eligible for a medical countermeasure Priority Review Voucher

Opaganib's development continues for COVID-19, other pandemic preparedness antiviral indications and oncology, strongly positioning opaganib as a major pipeline-in-a-product intended for multiple indications

TEL AVIV, Israel and RALEIGH, NC, Nov. 14, 2022 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced acceleration of opaganib's development program for protection against radiation injury and cancer radiotherapy. A recent publication in the **International Journal of Molecular Sciences, entitled "Opaganib Protects against Radiation Toxicity: Implications for Homeland Security and Antitumor Radiotherapy"**, describes the collective results of eight U.S. government-funded in vivo studies by RedHill and Apogee Biotechnology Corporation ("Apogee"), as well as additional experiments, establishing opaganib's[1] potential nuclear radiation protection capabilities[2].

The publication highlights observations from numerous studies undertaken in both protection against radiation toxicity and cancer radiotherapy settings. In the relevant study models, opaganib was associated with protection of normal tissue, including gastrointestinal, from radiation damage due to ionizing radiation exposure or cancer radiotherapy, as well as improvement of antitumor activity, response to chemoradiation, and enhancement of tolerability and survival. Additional independent studies demonstrate the radioprotective capacity of opaganib in bone marrow, with opaganib showing enhanced survival in mice which were irradiated with both lethal and half-lethal whole-body radiation[3].

"Subject to further alignment with FDA, we intend to follow the Animal Rule path to approval for opaganib, based on prior FDA guidance specific to opaganib for the intended indication. Development for medical countermeasures may follow the Animal Rule, with pivotal animal model studies of efficacy applicable when human clinical trials are not ethical or feasible. In addition, we intend to seek an expedited development timeframe and eligibility for a

Medical Counter Measure Priority Review Voucher. Amid the growing awareness of the need for material threat medical countermeasures and the positive observations seen in these in vivo gastrointestinal focused radiation toxicity and cancer radiotherapy studies, along with external data indicating potential radioprotective capacity of opaganib in bone marrow, we have accelerated our development plans to further test opaganib as a protective agent against nuclear radiation toxicity. We have recently initiated a new study to assess protective effects of opaganib on radiation-induced hematologic and renal toxicity, with our partner Apogee. Another meeting with the FDA is scheduled to seek further guidance on the path to homeland security medical countermeasure approval. Discussions with multiple government agencies in the U.S. and internationally, regarding funding and other governmental support, have been initiated," **said Gilead Raday, Chief Operating Officer and Head of R&D at RedHill**. "Importantly, opaganib has demonstrated its safety and tolerability profile in more than 470 people in studies in other indications as well as expanded access use. As an oral, small molecule pill that is highly stable with a greater than five-year shelf-life, opaganib is easy to administer and distribute, supporting potential central countermeasures stockpiling by governments."

Mitigation of radiation toxicity is an area of governmental concern. A key priority for US government research efforts is focused on finding long shelf-life and easy to distribute and administer drugs for potential inclusion in the Strategic National Stockpile. Such drugs, to be used in mass casualty nuclear radiation incidents involving improvised nuclear or radiological dispersal devices, should have broad-acting protective capability, be able to be administered 24 hours or later after radiation exposure, be safe and be easy to distribute to large numbers of people needing treatment for the acute effects of high dose, whole-body radiation exposure.

Currently, to the best of the Company's knowledge, only four FDA-approved medical countermeasure therapies are available. Three of these options are limited to effects caused by a small number of specific radioactive materials or to specific parts of the body. Potassium iodide (iodine pills) is intended to be used to protect against thyroid damage from the release of radioiodine. It works by preventing the thyroid from taking up radioactive iodine but seems to offer no protection to the rest of the body from irradiation and is of limited benefit unless given immediately upon exposure. The other two, Prussian Blue and DTPA (diethylenetriamine pentaacetate) provide protection by limiting the half-life in the body of specific materials: radioactive cesium and thallium, in the case of Prussian Blue, and radioactive plutonium, americium, and curium, in the case of DTPA. The fourth option, filgrastim, is intended for acute radiation syndrome resulting from high-dose radiation. Filgrastim does not seem to protect the body against the radiation itself and works by stimulating the creation of new white blood cells to protect the body from infections, which the body can no longer do in the presence of radiation-induced bone marrow destruction - as long as there are viable stem cells to stimulate.

We believe that opaganib's protection would not be limited to specific radioactive materials or individual parts of the body. Much of the damage caused by radiation exposure is caused by inflammation secondary to the effects of

ionizing radiation itself – known as Acute Radiation Syndrome. Opaganib, a sphingosine kinase-2 (SK2) inhibitor, is thought to exert its protective effects via an anti-inflammatory mechanism of action involving ceramide elevation and reduction of sphingosine 1-phosphate (S1P) in human cells - suppressing inflammatory damage to normal tissue and thus suppressing toxicity from unintended ionizing radiation exposure. It has also been reported in the literature that inhibition of sphingosine kinase 2 promotes the viability and robustness of hematopoietic stem cells, even in the face of radiation damage, supporting increased survival.

Protection against radiation toxicity studies with opaganib funded by U.S. government – summary of results:

Effect of opaganib on the lethality of TBI (Total Body Irradiation) in C57BL/6 mice

Vehicle-treated mice had pronounced symptoms indicative of severe GI damage, and all animals had to be euthanized within 14 days of radiation exposure. In contrast, protection was observed in the opaganib-treated group, in which 71% of the mice survived indefinitely.

Accumulation and pharmacodynamics of opaganib in mouse small intestine

In vehicle-treated mice, TNFα expression in the small intestines was observed to be up-regulated as early as 1 hour after Total Body Irradiation (TBI) and remained highly elevated for at least 26 hours. In contrast, pretreatment with opaganib was observed to not only block the induction of TNFα by TBI but also to reduce tissue TNFα levels below the baseline level indicating prolonged biodistribution of opaganib into the small intestine at sufficient levels to inhibit SK2 and suppress radiation-induced inflammation.

Effects of opaganib on GI damage following TBI

Post-radiation decreases in villus height (villi are a critical component of the intestines ability to absorb nutrients and indicative of intestinal health) were observed in the vehicle-treated animals compared with non-irradiated controls. In contrast, villus height was maintained in the opaganib-treated mice. Additionally, while there was evidence of cell depletion after 10 days in all groups, there were significantly more cells present at 4 days after irradiation in the opaganib-treated mice compared to vehicle controls ($p<0.001$) with this difference between treatments nearly resolving by Day 10.

Effect of opaganib on the lethality of partially shielded irradiation in C57BL/6 mice

In multiple scenarios, utilizing partial bone marrow shielding, involving different levels of irradiation and with different dosing regimens, opaganib was observed to reduce mortality, with the greatest improvement seen when opaganib was given both before and after irradiation, reducing mortality from 82% down to 4% ($p<0.001$) in the

mice given the highest dose of radiation, 16 Gray (Gy).

Cancer radiotherapy studies with opaganib funded by U.S. government – summary of results:

In vitro effects of opaganib on cell radiosensitivity

Opaganib appeared to provide protection from IR-induced cell death, with observations showing the level of radiation need to kill 50% and 90% of intestinal epithelial cells increasing from 5.56 and 12.16 Gy respectively up to 6.46 and 13.2 Gy, respectively. Furthermore, opaganib was observed to increase the killing of transformed pancreatic cancer cells by radiation, particularly at the high dose of 15 Gy ($p<0.05$).

In vivo effects of combination of opaganib with radiation on tumor growth (multiple cancer-types):

Pancreatic cancer model: Treatment with either TBI alone or opaganib alone substantially reduced tumor growth ($p<0.05$ and $p<0.001$, respectively). Treatment with opaganib in combination with TBI was associated with significantly reduced tumor growth compared to the control group or to the TBI alone group ($p<0.01$ for each comparison) but was not significantly different from opaganib alone because of the strong antitumor activity of the drug in this model. Importantly, treatment with opaganib did not protect tumors from radiation treatment.

Melanoma and E0771 breast cancer model: Opaganib plus TBI was observed to have equal or better antitumor activity than TBI alone. Again, opaganib was not associated with a diminished tumor response to fractionated radiation treatment and increased weight loss from radiation treatment was not observed.

Head & neck cancer model: Treatment with opaganib alone was observed to slightly reduce tumor growth, while TBI + cisplatin was observed to substantially reduce tumor growth as compared to the control (vehicle) group ($p<0.001$). Treatment with opaganib in combination with TBI + cisplatin was associated with the greatest reduction in tumor growth and such treatment group had significantly better observations than TBI + cisplatin on Day 21 and after ($p<0.02$). Again, opaganib was not associated with diminished tumor response or increased weight loss.

About Opaganib (ABC294640)

Opaganib a new chemical entity, is an orally administered, first-in-class proprietary selective inhibitor of sphingosine kinase-2 (SK2) with suggested anti-inflammatory, anticancer, radioprotective and antiviral activity.

Opaganib is thought to work through the inhibition of multiple pathways, the induction of autophagy and apoptosis, and disruption of viral replication, through simultaneous inhibition of three sphingolipid-metabolizing enzymes in human cells (SK2, DES1 and GCS).

In an oncology & radiological setting, opaganib has been observed to elevate ceramide and reduces sphingosine 1-phosphate (S1P) in cells, conditions that increase the antitumor efficacy of radiation while concomitantly suppressing inflammatory damage to normal tissue, leading to the potential to suppress toxicity from unintended ionizing radiation (IR) exposure and improve patient response to chemoradiation. Opaganib has 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. Patient accrual, treatment and analysis in a prostate cancer study is ongoing. Opaganib has a Phase 1 chemoradiotherapy study protocol ready for IND submission.

Opaganib has demonstrated broad-acting, host-directed, antiviral activity against SARS-CoV-2, multiple variants, and several other viruses, such as Influenza A. Being host-targeted, and based on data accumulated to date, opaganib is expected to maintain effect against emerging viral variants. In prespecified analyses of Phase 2/3 clinical data in hospitalized patients with moderate to severe COVID-19, oral opaganib demonstrated improved viral RNA clearance, faster time to recovery and significant mortality reduction in key patient subpopulations versus placebo on top of standard of care. Data from the opaganib global Phase 2/3 study has been submitted for peer review and recently published in **medRxiv**.

Opaganib has also shown positive preclinical results in renal fibrosis, and has the potential to target multiple oncology, radioprotection, viral, inflammatory, and gastrointestinal indications.

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[4], **Talicia®** for the treatment of Helicobacter pylori (H. pylori) infection in adults[5], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[6]. 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 broad-acting, host-directed, SK2 selective inhibitor targeting multiple indications, including for pandemic preparedness, with a Phase 2/3 program for hospitalized COVID-19 and a Phase 2 program in oncology and a radiation protection program ongoing; (iii) **RHB-107** (**upamostat**), an oral broad-acting, host-directed serine protease inhibitor with potential for pandemic preparedness and is in Phase 3-stage development as treatment for non-hospitalized 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; and (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. More information about the Company is available at **www.redhillbio.com**/ **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 opaganib will not be shown to elevate ceramide and reduce sphingosine 1-phosphate (S1P) in cells, increasing the antitumor efficacy of radiation while concomitantly suppressing inflammatory damage to normal tissue, leading to the potential to suppress toxicity from unintended ionizing radiation (IR) exposure and improve patient response to chemoradiation in an oncology & radiological setting, the risk that the FDA does not agree with the Company's proposed development plans for opaganib for any indication, the risk that observations from preclinical studies are not indicative or predictive of results in clinical trials, the risk that opaganib will not be shown to be broad acting, host-directed candidate therapies for pandemic preparedness, the risk that a pivotal Phase 3 trial for opaganib will not be initiated or that such trial be successful and, even if successful, such study and results may not be sufficient for regulatory applications, including emergency use or marketing applications, and that additional COVID-19 studies for opaganib are required by regulatory authorities to support such potential applications and the use or marketing of opaganib for COVID-19 patients, that opaganib 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 17, 2022, and the Company's Report on Form 6-K filed with the SEC on November 10, 2022. 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.

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Category: R&D

[1] Opaganib is an investigational new drug, not available for commercial distribution.
[2] Maines LW, Schrecengost RS, Zhuang Y, Keller SN, Smith RA, Green CL, Smith CD. Opaganib Protects against Radiation Toxicity: Implications for Homeland Security and Antitumor Radiotherapy. International Journal of Molecular Sciences. 2022; 23(21):13191. **https://doi.org/10.3390/ijms232113191**.
[3] Li C. et al., Loss of Sphingosine Kinase 2 Promotes the Expansion of Hematopoietic Stem Cells by Improving Their Metabolic Fitness. Blood. October 2022;140(15):1686-1701.
[4] Movantik® (naloxegol) is indicated for opioid-induced constipation (OIC). Full prescribing information see: **www.movantik.com**
[5] Talicia® (omeprazole magnesium, amoxicillin and rifabutin) is indicated for the treatment of H. pylori infection in adults. For full prescribing information see: **www.Talicia.com**.
[6] Aemcolo® (rifamycin) is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of Escherichia coli in adults. For full prescribing information see: **www.aemcolo.com**.

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