NEWS RELEASE

RedHill Biopharma Announces Positive FDA Meeting Regarding Opaganib for Acute Nuclear Radiation Syndrome

2/15/2023

FDA provided guidance on opaganib's regulatory pathway under the Animal Rule for Acute Radiation Syndrome (ARS)

The FDA's Animal Rule allows for the use of pivotal animal model efficacy studies to support FDA approval of new drugs when human clinical trials are not ethical or feasible

Opaganib is an oral, novel, highly stable, small molecule pill with a five-year shelf life that is potentially suitable, if approved, for central stockpiling by governments against mass casualty nuclear radiation incidents

RedHill plans to work closely with the FDA on development of opaganib as a nuclear medical countermeasure and is set to continue to collaborate with a range of U.S. agencies and other governments on this and other indications

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

TEL AVIV, Israel and RALEIGH, N.C., Feb. 15, 2023 /PRNewswire/ -- **RedHill Biopharma Ltd.** (Nasdaq: RDHL) ("RedHill" or the "Company"), a specialty biopharmaceutical company, today announced the positive outcome of a scheduled Type B meeting with the U.S. Food and Drug Administration (FDA) for the development of opaganib for Acute

Radiation Syndrome (ARS) in which the FDA provided guidance on opaganib's developmental pathway to potential approval under the Animal Rule.

"We are pleased to align with the FDA on the Animal Rule development pathway for opaganib for ARS. The FDA has provided very helpful guidance regarding the applicability in the case of opaganib of pivotal animal model efficacy studies in place of human clinical trials, and we plan to work closely with them to advance the development program in support of opaganib as a nuclear medical countermeasure," **said Dr Mark Levitt, MD, PhD, Chief Scientific Officer at RedHill**. "Given the promising data already generated with opaganib for ARS, we are set to continue collaborating with a range of U.S. agencies in addition to discussions with other governments."

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 preclinical in vivo studies by RedHill and Apogee Biotechnology Corporation ("Apogee"), as well as additional experiments, indicating opaganib's[1] potential nuclear radiation protection capabilities[2]. In the relevant study models, opaganib was associated with protection of normal tissue, including gastrointestinal tissue, from radiation damage due to ionizing radiation exposure or cancer radiotherapy. Additional independent studies demonstrate the potential role of inhibition of sphingosine kinase-2 in radioprotection in bone marrow, with knockout of sphingosine kinase-2 correlated with enhanced survival following both lethal and half-lethal whole-body radiation[3]. Sphingosine kinase-2 is the target of opaganib. Opaganib's protection is not expected to be limited to specific radioactive materials or individual parts of the body.

Opaganib, an oral, small molecule pill with a five-year shelf-life, is easy to administer and distribute, supporting, if approved, potential central government stockpiling for use in mass casualty nuclear radiation incidents. Sponsors of approved medical countermeasures are eligible for a Priority Review Voucher.

About Acute Radiation Syndrome (ARS)

ARS, sometimes known as radiation toxicity or radiation sickness, is generally rare; however, one event, such as a nuclear power plant disaster, can affect very large numbers of people. ARS is an acute illness caused by irradiation of the body by a high dose of penetrating radiation in a short period of time (usually a matter of minutes). Much of the damage caused by ARS is caused by inflammation secondary to the effects of ionizing radiation itself.

There are four stages of ARS:

Prodromal stage – characterized by nausea, vomiting, anorexia and diarrhea (depending on dose), occurring within minutes to days post-exposure
Latent stage – where the patient may look and feel generally healthy for a period lasting from a few hours up to a

few weeks
Manifest illness stage – symptoms for which can vary according to the focus of the radiation damage (i.e. bone marrow, gastrointestinal, cardiovascular, etc.) and can last from hours up to several months
Recovery or death - most patients who do not recover are expected to die within several months, or less, of exposure
Current treatment of ARS is generally limited to supportive care, including blood transfusions, antibiotics, colony-stimulating factors, or stem cell transplantation – with very few options available to treat or prevent the damage caused by radiation exposure. Opaganib, which may offer a new therapeutic approach, is a sphingosine kinase-2 (SK2) inhibitor 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 the possibility of increased survival.

About the FDA Animal Rule

The use of the Animal Rule is intended for drugs developed to reduce or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances.

The Animal Rule allows for the use of pivotal animal model efficacy studies when human clinical trials are not ethical or feasible. In such cases efficacy is established using well-controlled studies in animal models of the human disease, with safety being evaluated under the preexisting requirements for drugs.

Products approved under the Animal Rule are critical for the protection of public health and national security, and to date 13 drugs have previously been approved under the Animal Rule.

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 ARS setting, opaganib 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.

Opaganib is also being developed as a host-directed antiviral against SARS-CoV-2 and other viruses, has received Orphan Drug designation from the U.S. FDA for the treatment of cholangiocarcinoma and has undergone a Phase 2a study in advanced cholangiocarcinoma and a prostate cancer study is ongoing. Opaganib also 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, **Talicia®** for the treatment of Helicobacter pylori (H. pylori) infection in adults[4], and **Aemcolo®** for the treatment of travelers' diarrhea in adults[5]. 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, is in late-stage development for treatment of non-hospitalized symptomatic COVID-19, and is 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 expected UK submission for chemotherapy and radiotherapy induced nausea and vomiting, 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 the Company will not be successful in collaborating with U.S. agencies and other governments, 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.

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

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] 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**.

[5] 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**.

Logo - **https://mma.prnewswire.com/media/1334141/RedHill_Biopharma_Logo.jpg**

View original content:**https://www.prnewswire.com/news-releases/redhill-biopharma-announces-positive-fda-meeting-regarding-opaganib-for-acute-nuclear-radiation-syndrome-301747424.html**

SOURCE RedHill Biopharma Ltd.