Emergency Use-Treatment IND Protocol Study# BHC-RIB-5401
VIRAZOLE® (Ribavirin for Inhalation Solution, USP)

Compassionate Use Study Synopsis

Title: An Open-label Compassionate Use Study to Evaluate the Safety and Efficacy of VIRAZOLE® (Ribavirin for Inhalation Solution, USP) in Hospitalized Adult Participants with Respiratory Distress Due to SARS-CoV-2 (COVID-19).

Brief Summary:

This study is an open label, interventional compassionate use study to evaluate the safety and efficacy of an approved therapeutic agent (approved in infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV)) in hospitalized adult patients who have tested positive for SARS-CoV-2 (COVID-19) and as a result have significant respiratory distress (PaO_2/FiO_2 ratio < 300 mmHg). The study will consist of 1active treatment (no placebo), while allowing the subjects to continue receiving standard of care. Emergency Use treatment will be on per patient basis/physician-investigator. Subjects will be assessed daily while hospitalized will undergo a series of efficacy and safety assessments.

The primary objective of the study is to evaluate the clinical activity of VIRAZOLE® (Ribavirin for Inhalation Solution, USP) in eradication of SARS-COV-2 (COVID-19) using 2 dosing regimens in subjects with confirmed COVID-19 infections and diagnosed with respiratory distress (PaO_2/FiO_2 ratio < 300 mmHg).

Study Type:	Compassionate Use; Hospitalized
Treatment Allocation:	Emergency Use per patient basis /physician
Masking:	None (Open Label)
Primary Purpose:	Activity in patients with SARS-COV-2 (COVID-19)
Study Start Date:	April, 2020
Estimated Completion:	March, 2021

Treatment:

The treating physician, based on clinical judgement, can use the experimental dosing regimen below or tailor the dosing regimen based for each hospitalized patient.

VIRAZOLE® Treatment Regimen	VIRAZOLE® inhalation solution prepared for aerosolization at 100 mg/ml Participants will receive continued standard of care together with VIRAZOLE® aerosolized solution 100 mg/ml for 30 minutes, twice a day for up to 6 Days.

Clinical Study Endpoints:

Primary Outcome Measure:

1. Change in clinical status severity (CSS) rating on the 7-point ordinal scale from the first dose date up to 6 days or date of Virazole discontinuation or death. Ordinal scale of clinical status:

    1) Death
    2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
    3) Hospitalized, on non-invasive ventilation or high flow oxygen devices
    4) Hospitalized, requiring supplemental oxygen
    5) Hospitalized, not requiring supplemental oxygen
    6) Not hospitalized, limitation on activities
    7) Not hospitalized, no limitations on activities.

Secondary Outcome Measures:

1. Time to recover gas exchange to a PaO_2/FiO_2 =/> 300 for at least 24 hours
2. Time to reach peripheral capillary oxygen saturation ($Sp0_2$) > 94% for at least 24 hours

Safety Outcome Measures:

Proportion of participants with treatment emergent adverse events (TEAEs) leading to study drug discontinuation.

Inclusion and Exclusion Criteria:

Key Inclusion Criteria:

- Male or non-pregnant female, age ≥ 18
- Willing and able to provide written informed consent (or provided by a proxy).
- Currently hospitalized with laboratory confirmed SARS-COV-2 (COVID-19) novel coronavirus infection
- PaO_2/FiO_2 ratio < 300 mmHg
- Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - Clinical assessment (evidence of rales/crackles on exam) AND SpO2 </= 94% on room air, OR
    - Requiring mechanical ventilation and/or supplemental oxygen.
- Women of childbearing potential must agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site).

Key Exclusion Criteria:

- Pregnancy or breast feeding
- Respiratory distress for reasons other than SARS-COV-2 (COVID-19) infection (e.g., CHF, bacterial pneumonia, etc.)
- Presence of significant pulmonary fibrosis
- Hypotension (need for hemodynamic pressors to maintain blood pressure)
- Greater than 7 days on mechanical ventilation
- Subject has any condition that could cause noncompliance with treatment or may otherwise contraindicate the subject's participation in the study
- Subject has a history of hypersensitivity to ribavirin

Appendix A

Experimental Dosing Regimen of Virazole Aerosol in SARS-COV-2 (COVID-19)

The current FDA-approved use of Virazole Aerosol is 20 mg/mL, obtained after dilution of one vial of 6g of ribavirin (75 mL of Sterile Water for Injection or Sterile Water for Inhalation) added into the 100mL vial before adding/diluting in 300mL/reservoir; refer to Prescribing Information for method of preparation) in the reservoir of a SPAG2 nebulizer with continuous exposure to the aerosol for 12-18 hours per day for 3 to 7 days. Using the recommended drug concentration of 20 mg/mL the average aerosol concentration for a 12-hour delivery period would be 190 mcg/L of air. This long, continuous treatment requirement can interfere with patient care. Using animal models, Gilbert and McLeay (Antiviral Research 78 (2008) 223–229) demonstrated that by increasing the ribavirin concentration in the reservoir, the time of treatment could be significantly reduced. When used **with the more efficient Aerotech II nebulizer**, once or twice daily treatments of a high dosing regimen of Virazole Inhalation solution (100 mg/mL in the reservoir) was studied and determined to be effective in preventing death in a lethal influenza A virus mouse model (A/HK/8/68 (H3N2)). The aerosol generated using the Aerotech II nebulizer flowing at 10 L of air/min produced aerosol droplets that contained 2.3 mg of ribavirin/L with a mass median aerodynamic diameter of 1.8 m. Using this system for treatment, a single daily 30-min exposure on days 1–4 produced a survival rate of greater than 90% a lethal influenza A virus mouse model (A/HK/8/68 (H3N2)).

For treatment of SARS-COV-2 (COVID-19), delivering Virazole at 100 mg/ml (10 mls in the reservoir) over 30 minutes will deliver a calculated1,760 ug/ml to the alveolar lining fluid which is 64X greater than half maximal response (EC50) against a clinical isolate of SARS-COV-2 (COVID-19) in vitro, which is 26.7 ug/ml.

It is not anticipated that the short 30-min aerosol treatment with high-dose Virazole will change the safety profile since the dose delivered is equal to or less than the other previously used aerosol treatment regimens.

Appendix B

Reconstitution of VIRAZOLE® (Ribavirin for Inhalation Solution, USP)

For patients who meet the study criteria, the treating physician, based on clinical judgement, can use the experimental dosing regimen below or tailor the dosing regimen based for each hospitalized patient.

A) 100 mg/ml* for 30 minutes (10 ml in reservoir) twice daily for up to 6 days
10 liters of O_2 per minute

**Dose limited by solubility*

VIRAZOLE for inhalation solution is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 mL glass vial contains 6 grams of ribavirin. Take steps to maintain sterility of the solution once reconstituted. Data on file supports stability of reconstituted product for 72 hours at room temperature.

For 100 mg/ml dosing: Reconstituted to the recommended volume of 60 mL with Sterile Water for Injection, USP or Sterile Water for Inhalation (no preservatives added), the vial will contain 100 mg of ribavirin per mL, pH approximately 5.5. Place 10 mls of the solution in the nebulizer reservoir. Shake well.