STUDY SYNOPSIS

NCT03926819

Date: January 30, 2023

Title of Study: A Phase 1 ascending single-dose followed by multiple dose safety and pharmacokinetic study of HBI-002 carbon monoxide liquid formulation in healthy adult volunteers.

Protocol Number: HBI-002-001

Investigators/Study Center:

Phase of Development: 1

Objectives/Endpoints:

Primary Objective/Endpoint: To assess the safety and tolerability of HBI-002, given as single ascending doses (SAD) and multiple doses (MD) daily for 7 days in healthy male and female adult subjects based on frequency and severity of TEAE, including adverse events of special interest.

Secondary Objectives/Endpoints:

1. To evaluate the pharmacokinetics (PK) of HBI-002 with increasing doses of oral HBI-002 as measured by COHb levels.
2. To determine the HBI-002 dose required to achieve peak COHb levels up to 10% within one hour after ingestion.
3. To evaluate any accumulation of CO as measured by COHb with daily dosing and to assess changes in venous lactate levels.
4. To evaluate biomarkers of inflammation and to assess changes induced by HBI-002.

Planned Sample Size:

Up to 16 subjects will be enrolled in the SAD phase (up to 4 dose cohorts) and 4 subjects in the MD phase (one dose cohort). Additional subjects (up to 8 in the SAD phase and up to 6 in the MD phase) may be enrolled in any cohort, as needed, if incomplete data is obtained or there is a need to obtain additional safety observations. Subjects in the MD cohort will be replaced if all 7 doses are not ingested or labs for safety assessment are not complete. Subjects will not be replaced in the event the subject discontinues the study due to a related adverse event.

Study Duration: Approximately 26 weeks

Study Design:

This is a single center, open-label trial investigating up to four single ascending doses (SAD), followed by a single cohort of multiple doses (MD) with dosing daily for 7 days. Both the SAD and MD dosing cohorts utilize an adaptive dosing regimen. Eligible healthy adult subjects who have signed the informed consent will undergo a screening assessment carried out within 4 weeks of study entry consisting of a medical history, concomitant medications, physical examination, height and weight, vital signs, ECG, hematology and chemistry labs, infectious disease screen including SARS-CoV-2, hemoglobin electrophoresis, urinalysis, pregnancy and drug screen.

Pregnancy testing in females of childbearing potential will be carried out in both the SAD and MD study components at screening and baseline, as well as in the SAD component at 48 hours and on Day 30, and in the MD component on Days 8 and 37.

Concomitant medications and adverse events will continue to be monitored to the final follow up visit.

<u>Dosing rules (SAD and MD)</u>

For the SAD study component, there will be at least 72 hours between dosing of the first study subject at each dose level and the subsequent 3 subjects at the same dose level and with no minimum time between dosing of each subsequent subject. There also will be at least 72 hours between the last subject at each dosing level and the first subject at the next dose level. For the MD study component,

there will be at least 30 days between the last subject at the final SAD dose level and the first subject in the MD dose level. For the MD dosing, there will be 72 hours between the first subject receiving the first MD dose and the subsequent 3 subjects at that dose level with no minimum time between dosing of the 3 subsequent subjects.

All subjects (SAD and MD)

Peak COHb measured by co-oximeter will be monitored for safety, targeting levels of no more than 10% COHb, and COHb saturation will be documented for each subject at all time points. The DSMB will review safety information through 72 hours after completion of dosing for each SAD cohort. The specific dose cohort at the next level, as designated under SAD dosing, may proceed provided that no related safety issues are observed.

The DSMB will review safety information after completion of dosing for all SAD cohorts at 30 days post-dosing of the final subject in the final SAD cohort. The safety and PK data from the SAD phase will be submitted to the FDA prior to the initiation of the MD phase. The MD phase will not be initiated until the FDA has approved of the advancement.

COHb measured by co-oximeter and venous lactate together with pH measurements will be carried out and reported within one hour of the respective blood draw for all study subjects. COHb, pH and lactate results will be provided to the PI and MM as soon as available, but not later than one hour after the respective blood draw.

Subjects will be released when all of the following criteria have been met.

1. COHb saturation by venous blood gas, venous lactate and pH at normal physiological levels.
2. Transcutaneous oxygen saturation at normal physiological level.
3. Normal vital signs and cardiac rhythm.
4. No adverse symptomatology.

Subjects demonstrating clinical or laboratory abnormalities at the designated final visit will continue to be followed until the abnormality is resolved or stabilized.

Stopping Rules

If any subject experiences signs or symptoms of CO toxicity as detailed below, further enrollment and dosing will be put on hold until the DSMB reviews relevant data and makes recommendations as to next steps. In addition, for the affected subject(s), that subject(s) will be discontinued and will immediately be administered oxygen. If the protocol is put on hold for any reason, Hillhurst will communicate DSMB recommendations to FDA before resuming enrollment.

Subjects will not be replaced if they discontinue the study due to an adverse event (AE).

Diagnosis and Key Subject Selection Criteria: Subjects who satisfy all of the inclusion and exclusion criteria below will be eligible to participate in the study.

Inclusion Criteria

1. Signed informed consent.
2. Healthy male or female 18-55 years of age inclusive.
3. Negative HBsAg, aHCV, aHIV, and SARS-CoV-2 test.
4. Non-smoker or vaper (no use of tobacco or marijuana products within 3 months of screening).
5. Body weight between 60 kg and 110 kg (inclusive) and with BMI less than 30 kg/m^2.
6. Subjects must be healthy as defined by:
   a. absence of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic or allergic disease, as determined by the Investigator.
   b. liver function: alanine transaminase (ALT) and aspartate transaminase (AST) ≤2 times the upper limit of the normal range

c. total bilirubin ≤1.5 times the upper limit of the normal range
d. renal function: creatinine clearance within normal range as assessed by Cockcroft and Gault calculation
e. carboxyhemoglobin level by venous blood gas ≤ 3.5% (any time prior to the first dose)
f. venous lactate level <2.0 mmol/L at baseline.
g. the absence of current clinically relevant abnormalities identified by a detailed medical history, full physical examination including blood pressure and pulse rate measurement, 12-lead ECG, and clinical laboratory tests (hematology and clinical chemistries), as determined by the Investigator.

7. Negative pregnancy tests for females.
8. Subjects must be willing to use a highly effective method of contraception for the duration of the study and for 30 days thereafter.
   a. Male subjects, without a vasectomy, must use a condom and be instructed that their female partner should use another form of contraception such as an IUD, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation if the female partner could become pregnant
   b. Female subjects of childbearing potential (not surgically sterilized and less than one year post-menopausal) should use a form of contraception such as an IUD, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation, and be instructed that their male partners should use a condom, if not vasectomized.

Exclusion Criteria

Subjects who meet any of the following criteria will be ineligible for participation in the study:

1. Subjects with concurrent illness/disease as defined by:
   a. clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic or allergic disease, as determined by the Investigator.
   b. current clinically relevant abnormalities identified by a detailed medical history, full physical examination including blood pressure and pulse rate measurement, 12-lead ECG, and clinical laboratory tests (hematology, clinical chemistries and urinalysis), as determined by the Investigator.
   c. clinically significant illness and/or surgery within 4 weeks prior to dosing.
2. Anemia of any cause.
3. Homozygous or heterozygous hemoglobinopathy.
4. Blood transfusion within six weeks prior to the first administration of study drug.
5. Carboxyhemoglobin ≥ 3.5% (any time prior to the first dose)
6. Oxygen saturation by transcutaneous measurement consistently ≤ 95% (any time prior to the first dose)
7. Exposure to any live vaccine within 28 days prior to study drug administration.
8. History of febrile or infective illness within 14 days prior to dosing.
9. Positive pregnancy test or breast feeding for females.
10. Weight loss or gain of more than 5 kg within 3 months prior to dosing.
11. History of alcohol abuse or dependence or regular use of alcohol within six months prior to dosing (defined as more than 14 units of alcohol per week; 1 Unit= 150 mL wine, 360 mL beer or 45 mL of 40% alcohol)
12. Positive result on alcohol screen
13. History of pulmonary infiltrate or pneumonia within 6 months prior to dosing or pulmonary/bronchial infection within 2 weeks prior to dosing.
14. History of cancer, with the exception of adequately treated basal cell or squamous cell carcinoma of the skin more than 1 year prior.
15. History of cardiac disease
16. History of drug abuse or dependence.

17. Positive results on drug screen (oxycodone, benzodiazepines, THC, cocaine, opiates, and methamphetamine).
18. Use of prescription drugs within 7 days or 5 half-lives (whichever is longer) prior to dosing. Herbal and vitamin supplements must be discontinued 14 days prior to dosing.
19. Unwilling or unable to comply with the requirements of the protocol.
20. Treatment with an investigational drug within the longer of 30 days or five half-lives.
21. Systolic blood pressure lower than 90 or above 140 mm Hg, diastolic blood pressure lower than 50 or above 90 mm Hg, heart rate less than 45 or above 100 bpm, or arrhythmia at screening and/or baseline. ECG abnormalities or other vital sign abnormalities that are clinically significant at screening and/or baseline, as determined by the Investigator.
22. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into the study.
23. History of allergic reactions to any of the drug product excipients
24. History of epilepsy or seizure
25. History of suicide attempts or ideation (by medical history)

Criteria for Evaluation/Statistical Methods:

Pharmacokinetics:

PK will be assessed in each subject based on whole blood COHb levels obtained at each designated blood draw. PK will be assessed on each subject in the SAD phase and on each subject in the MD phase with COHb. In the MD phase, PK analysis will be carried out on both the first and final dose of HBI-002. Standard pharmacokinetic parameters for COHb incremental recovery [IR], maximum concentration following oral administration [Cmax], time to reach Cmax [Tmax], terminal or disposition half-life [t1/2], mean residence time [MRT], systemic clearance [Cl/F], area under the whole blood-time curve [AUC] and volume of distribution [Vd/F] after single oral administrations of HBI-002 at each dose level. The PK concentration data at each timepoint will be listed for each subject and summarized by dose level using descriptive statistics. Individual subject and mean concentration-time data will be graphically presented separately. If sufficient data are available across SAD dose cohorts, dose proportionality will be evaluated using a power model.

PK analyses will use the actual observed sample drawing times. Samples with unknown drawing time and/or where the concentration could not be determined will be eliminated from the calculations. Concentration data will be carried out in two modes: No correction for baseline value and corrected for baseline by subtraction of the mean pre-dosing value.

PK parameters will be derived using noncompartmental methods with appropriate software. The following parameters will be calculated for each patient separately: AUC, IR, Cmax, AUCinf, Tmax, $t_{1/2}$, MRT, Clearance (CL/F) and Vd/F. These parameters will be summarized for each Dose Cohort separately by using descriptive statistics (number, mean, standard deviation, minimum, maximum, median, coefficient of variation, geometric mean and the corresponding 90% confidence intervals as appropriate).

Safety:

All safety data will be included in the subject data listings. Summary tables will be based upon the safety population.

Serious and non-serious adverse events, occurring up to 30 days after the last oral dose will be tabulated and summarized according to the most recent version of the MedDRA. Frequencies and percentages of subjects experiencing at least one event will be summarized by system organ class and preferred term for all AEs, for AEs considered to be possibly or probably related to the study drug, and for SAEs. The number and proportion of subjects experiencing these events will be tabulated by dose for each study phase (SAD or MD). Related adverse events will be listed.

Individual and summary vital signs and clinical laboratory data will be presented for each study phase in tabular form with mean, standard deviation and range as appropriate.

For the vital signs, transcutaneous oxygen concentration, venous COHb and other laboratory safety data, and ECG data, out of range values considered to be clinically significant will be flagged in the data listings and a separate listing of clinically significant abnormal values will be presented, including any COHb value >10%.