2. SYNOPSIS

STUDY TITLE: A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-BGB-11417 Following Single Oral Dose Administration in Healthy Male Subjects

INVESTIGATOR: [redacted]

STUDY SITE(S): 1 clinical site in the United States

PUBLICATION (REFERENCE): None

STUDY PERIOD:
09 June 2023 (date of first subject first dose) to 06 July 2023 (date of last subject contact)

PHASE OF DEVELOPMENT: 1

OBJECTIVES:
The primary objectives of this study were:

- To determine mass balance and routes of elimination of [^{14}C]-sonrotoclax (also known as [^{14}C]-BGB-11417) in healthy male subjects
- To assess the pharmacokinetics (PK) of a single dose of 20 mg sonrotoclax using [^{14}C]-labeled sonrotoclax (100 µCi [3.7 MBq])
- To determine the whole blood and plasma concentrations of total radioactivity
- To determine the urinary and fecal recovery of total radioactivity

The secondary objectives of this study were:

- To characterize and identify metabolites of [^{14}C]-sonrotoclax in plasma, urine, and feces
- To determine plasma and urine concentrations of sonrotoclax and/or its potential major metabolites
- To assess the safety and tolerability of a single oral dose of [^{14}C]-sonrotoclax in healthy male subjects

METHODOLOGY:
This was a Phase 1, nonrandomized, open-label, single-dose, mass balance study designed to evaluate the absorption, metabolism, and excretion of [^{14}C]-radiolabeled sonrotoclax after oral administration. Healthy male subjects 18 to 65 years of age, inclusive, were enrolled and received a single oral dose of 20 mg [^{14}C]-sonrotoclax containing a total dose of radioactivity of 100 µCi (3.7 MBq). A minimum of 6 subjects were expected to complete the study. A subject who completed all PK, radioactivity, and metabolism sampling prior to clinic discharge was considered to have completed the study.

Subjects were screened for enrollment within a period of 21 days prior to dosing and eligible subjects checked into the clinic on the day before dosing (Day –1). Subjects received a single oral dose of liquid formulation of [^{14}C]-sonrotoclax in the morning on Day 1 following an overnight fast of at least 8 hours. Subjects remained fasted for 4 hours after dosing with study drug.

Blood, urine, and feces were collected. Whole blood, plasma, urine, and fecal samples were assessed for total radioactivity and were sent for radioisotope analysis after each 24-hour postdose interval. Plasma and urine samples were assayed for concentrations of sonrotoclax

and/or its potential major metabolites. Plasma, urine, and fecal samples were each pooled for quantitative metabolite radioprofiling and metabolite characterization and identification.

Safety assessments (collection of adverse events [AEs], clinical laboratory evaluations, vital signs, electrocardiograms [ECGs], and physical examination) were performed according to the schedule of events. Clinical laboratory tests were repeated at the discretion of the investigator, if necessary, for assessment of inclusion and exclusion criteria or evaluation of clinical laboratory abnormalities.

Number of subjects (planned and analyzed):

Enrollment of 6 healthy male subjects was planned. A total of 6 subjects were enrolled, and 6 (100%) completed the study. All 6 subjects (100%) were included in the PK and Safety populations.

Diagnosis and main criteria for inclusion:

Subjects were healthy males who were 18 to 65 years of age, inclusive, and had a body mass index of 18.0 to 35.0 kg/m^2, inclusive, at screening.

Test product, dose, and mode of administration, batch number:

- 20 mg [^{14}C]-sonrotoclax containing a total dose of radioactivity of 100 µCi (3.7 MBq), administered orally in a liquid formulation under fasted conditions, batch number: ABN-1576

Reference therapy, dose, and mode of administration, batch number:

- Not applicable

Duration of treatment:

Each subject remained confined to the clinical unit from Day −1 until at least 7 days after dosing and until one of the following release criteria were met:

- ≥ 90% of the administered radioactive dose was recovered, or
- < 1% of the administered radioactive dose was recovered in the subject's urine and/or fecal samples per day for 2 sequential days

Collection of urine and/or fecal samples continued in 24-hour intervals for [^{14}C] analysis until release criteria were met. Blood samples were collected every 24 hours until discharge.

The duration of the study for each individual subject, excluding screening, was expected to be approximately 12 days. The duration of the study was from the day that the first subject signed a consent form (start of study) through the day that all required study assessments were completed for the last subject (end of study).

CRITERIA FOR EVALUATION:

Pharmacokinetics:

PK samples and radioanalytical samples were obtained through at least 168 hours after dosing and as needed until discharge criteria for radioactivity were met, whichever came later.

Blood was collected through 168 hours after study drug administration according to the following schedule:

- Blood samples for assessment of PK and total radioactivity in whole blood and plasma: before dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing.
- Blood samples for metabolite profiling and identification in plasma: 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, and 144 hours after dosing.

Urine and feces were collected through at least 168 hours after study drug administration according to the following schedule:

- Urine samples for assessment of sonrotoclax concentration and total radioactivity and metabolite profiling and identification: Day −1 (from time of Check-in within approximately 18 hours before dosing) and after dosing at intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours.
- Fecal samples for assessment of total radioactivity and metabolite profiling and identification: Day −1 (from time of Check-in within approximately 18 hours before dosing) and after dosing at intervals of 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, and 144 to 168 hours

After collection of the 144- to 168-hour urine and fecal samples, if documentation was not available confirming at least 90% cumulative recovery of the [^{14}C] dose administered, collection of urine and/or fecal samples continued in 24-hour intervals for [^{14}C] analysis until a combined radioactivity of less than 1% of the administered dose was recovered per day for 2 sequential days. Blood samples were collected every 24 hours until discharge.

Whole blood, plasma, urine, and fecal samples were assessed for total radioactivity. Plasma and urine samples were assayed for sonrotoclax concentrations and/or its potential major metabolites. Plasma, urine, and fecal samples were each pooled for quantitative metabolite radioprofiling and metabolite characterization and identification.

The following PK parameters were from total radioactivity in whole blood and plasma and sonrotoclax in plasma using noncompartmental methods: area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), AUC from time 0 extrapolated to infinity (AUC_{0-inf}), percentage of area extrapolated between AUC_{0-t} to AUC_{0-inf} ($\%AUC_{extrap}$), apparent terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F; for sonrotoclax only), apparent volume of distribution (V_z/F; for sonrotoclax only), AUC Blood/Plasma Ratio = AUC_{0-t} of total radioactivity in whole blood/AUC_{0-t} of total radioactivity in plasma, and AUC Plasma sonrotoclax/Total Radioactivity Ratio = AUC_{0-t} of nonradiolabeled sonrotoclax in plasma/AUC_{0-t} of total radioactivity in plasma.

The following PK parameters were determined based on the urine concentrations of sonrotoclax and total radioactivity: amount excreted in urine per sampling interval (A_{eu}),

cumulative amount excreted in urine (Cum A_{eu}), renal clearance (CL_R; for sonrotoclax only), percentage of drug or radioactive dose excreted in urine per sampling interval ($\%F_{eu}$), and cumulative percentage of drug or radioactive dose excreted in urine (Cum $\%F_{eu}$).

The following PK parameters were determined from total radioactivity in feces: amount excreted in feces per sampling interval (A_{ef}), cumulative amount excreted in feces (Cum A_{ef}), percentage of radioactive dose excreted in feces per sampling interval ($\%F_{ef}$), and cumulative percentage of radioactive dose excreted in feces (Cum $\%F_{ef}$).

Metabolite profiling and identification was conducted by WuXi AppTec (Cranbury, NJ) using standard laboratory procedures and will be reported separately.

Safety:

Safety and tolerability were assessed by the following: adverse events, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECGs, and physical examination findings.

STATISTICAL METHODS:

Pharmacokinetics:

The individual concentration versus actual time data for total radioactivity and sonrotoclax were used to determine whole blood and plasma PK parameters using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.3 or higher. Urine PK parameters were calculated using SAS Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).

Total radioactivity in whole blood and plasma and concentrations of sonrotoclax in plasma were listed and summarized by timepoint. Mean whole blood and plasma concentration data for total radioactivity and mean plasma concentration data for sonrotoclax by nominal time profiles were provided on both linear and semilogarithmic scales. Individual whole blood and plasma concentration for total radioactivity and plasma concentration for sonrotoclax by actual sampling time profiles were provided on both linear and semilogarithmic scales.

Individual urine and fecal concentration data, sample volumes, and amounts of total radioactivity were listed by time interval. The amount recovered was also summarized for each collection interval and the overall collection period. Figures for individual and mean cumulative urine and fecal recovery (expressed as a percentage of dose) for total radioactivity by time interval were provided.

PK parameters derived from whole blood, plasma, urine, and fecal samples were presented in data listings and summarized separately using the following descriptive statistics: N, arithmetic and geometric means, SD, arithmetic and geometric coefficient of variation, median, minimum, and maximum.

A full description of the analysis was provided in the statistical analysis plan.

Safety:

Adverse events were coded by system organ class and preferred term using the latest version of Medical Dictionary for Regulatory Activities. All adverse event data were presented in a data listing. Adverse events were summarized by system organ class and preferred term, as well as by severity and relationship to study drug. Serious adverse events and adverse events leading to study discontinuation were also presented in the data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results were summarized at each timepoint using descriptive statistics (N, mean, SD, median, minimum, and maximum). Shift tables were generated for clinical laboratory test results. Physical examination findings were presented in a data listing.

RESULTS:

Pharmacokinetic Results:

Following a single oral administration of 20 mg of sonrotoclax containing 100 µCi of [^{14}C]-sonrotoclax, the mean concentration-time profile for sonrotoclax was characterized by a rapid absorption phase, typically reaching a peak 2 hours postdose. Thereafter, concentrations declined to levels below the limit of quantification beyond 168 hours postdose, with a geometric mean $t_{1/2}$ of 32.6 hours.

The mean concentration-time profile for total radioactivity in whole blood generally paralleled that in plasma, typically reaching a peak 1.75 to 2 hours postdose. Since concentrations declined to levels below the limit of quantification beyond 12 hours postdose, the terminal $t_{1/2}$ was estimated to be 4.4 hours in plasma and 5.28 hours in blood, which were shorter than the $t_{1/2}$ of unchanged sonrotoclax. Moderate to high inter-subject variability was observed in C_{max}, AUC_{0-t}, and AUC_{0-inf} values; coefficient of variation for plasma concentrations ranged from 50.0% to 57.5%.

The geometric mean peak (C_{max}) and exposure (AUC_{0-t}) for total radioactivity were slightly higher in plasma compared to whole blood. The blood to plasma ratio based on C_{max} ($C_{maxBlood}/C_{maxPlasma}$) was 0.684, and the blood to plasma ratio based on AUC_{0-t} (AUC_{Blood}/AUC_{Plasma}) was 0.738, suggesting low association of radioactivity with red blood cells.

Compared to plasma total radioactivity exposure, unchanged sonrotoclax exposure was approximately 72.6% for AUC_{0-t} (AUC_{BGB}/AUC_{TRA}), indicating that majority of total radioactivity in plasma was not associated with metabolites and sonrotoclax was the most abundant circulating entity.

The arithmetic mean recovery in urine was 0.238% of the administered dose, and the arithmetic mean recovery in feces was 86.2% of the administered dose through 216 hours postdose. Most of the administered radioactivity was recovered in the first 72 hours postdose (0.238% in urine, 77.4% in feces). Levels of radioactivity in urine were below the limit of quantitation for all subjects by 24 hours postdose. Levels of radioactivity in feces were quantifiable for all subjects through the last collection interval up to 168 to 192 hours. The overall mean total recovery in urine and feces samples was 86.4%, with recovery in individual subjects ranging from 64.1% to 103%. Two subjects had less than 80% of total radioactivity recovered and other 4 subjects had close to 90% or higher of total radioactivity recovered. The lower recovery may be due to potential sample lost and radioactivity lost during re-processing of samples.

The amount of unchanged sonrotoclax excreted in urine was 0.0073 mg corresponding to 0.036% of the 20 mg dose. The amount of unchanged sonrotoclax in urine was 15% of the mean cumulative amount of total radioactivity value in urine.

Safety Results:

Overall, 1 subject (16.7%) reported 1 treatment-emergent adverse event of Grade 1 diarrhea which was considered to be treatment related. There were no deaths or other serious adverse events reported during the study, and no subjects were discontinued from the study due to a treatment-emergent adverse event.

No individual hematology, serum chemistry, or urinalysis value was considered clinically significant or reported as a treatment-emergent adverse event by the investigator. One subject had experienced a Grade 2 decrease in neutrophils on Day 3, which normalized on Day 9. It was not considered clinically meaningful and hence not reported as a treatment-emergent adverse event. No individual vital sign measurement, physical examination finding, or abnormal ECG finding was reported as a treatment-emergent adverse event by the investigator.

CONCLUSIONS:

- Sonrotoclax was rapidly absorbed following a single oral dose of 20 mg sonrotoclax containing 100 μCi of [^{14}C]-sonrotoclax, with a median T_{max} of 2 hours. The geometric mean $t_{1/2}$ of sonrotoclax was 32.6 hours in plasma.
- The PK profiles for plasma and whole blood total radioactivity were similar. Total radioactivity appeared rapidly in plasma (median T_{max} = 2.0 hours) and whole blood (median T_{max} = 1.75 hours). The geometric mean $t_{1/2}$ values of total radioactivity were 4.40 hours in plasma and 5.28 hours in whole blood.
- The geometric mean whole blood/plasma AUC_{0-t} ratio for total radioactivity was 0.738, indicating low association of radioactivity with red blood cells.
- Based on AUC_{0-t}, unchanged sonrotoclax accounted for approximately 72.6% of the total radioactivity.
- Following oral administration, the arithmetic mean recovery of total radioactivity was 86.4%. The majority of administered radioactivity was recovered in feces (86.2%) with a small fraction recovered in urine (0.238%). The majority of radioactivity was recovered in the first 72 hours.
- A single oral dose of 20 mg sonrotoclax containing 100 μCi of [^{14}C]-sonrotoclax was safe and well tolerated by the healthy male subjects in the study.

DATE OF REPORT: 20 November 2023