2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Venetoclax, navitoclax		
Name of Active Ingredient: Venetoclax (ABT-199/GDC-0199), navitoclax (ABT-263)		
Title of Study: A Phase 1 Dose Escalation, Open-Label Study of Venetoclax in Combination with Navitoclax and Chemotherapy in Subjects with Relapsed/Refractory Acute Lymphoblastic Leukemia or Relapsed/Refractory Lymphoblastic Lymphoma		
Coordinating Investigator: [redacted]		
Study Sites: 14 sites in the United States and Australia		
Publications: 1 article, 9 abstracts		
Studied Period (Years): First Subject First Visit: 27 Nov 2017 Last Subject Last Visit: 14 Nov 2020	**Phase of Development:** 1	

Objectives:

The primary objectives of the study were:

- Evaluate the safety of venetoclax in combination with navitoclax
- Evaluate the safety of venetoclax in combination with navitoclax and chemotherapy
- Determine dose-limiting toxicities (DLTs) of venetoclax, navitoclax, and chemotherapy
- Assess the pharmacokinetics (PK) of venetoclax in combination with navitoclax

The secondary objectives of the study were:

- Determine the anti-tumor activity of venetoclax in combination with navitoclax
- Determine the anti-tumor activity of venetoclax, navitoclax, and chemotherapy, after the first cycle of chemotherapy
- Determine the number of subjects who proceeded to stem cell transplantation (SCT) or chimeric antigen receptor t-cell (CAR-T) therapy

Methodology:

This was an open-label, Phase 1 dose escalation study in pediatric and adult subjects with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) or R/R lymphoblastic lymphoma (LL). On Day 1, venetoclax was administered once daily (QD) at the 200 mg adult equivalent dose. On Day 2, venetoclax was administered QD at the 400 mg adult equivalent dose. Venetoclax was continued QD at the 400 mg adult equivalent dose for 37 weeks. All subjects received venetoclax, adjusted by weight, to match the exposure of the adult equivalent target doses.

For subjects in the dose escalation portion of the study, navitoclax QD dosing began on Day 3 and continued throughout the 37-week treatment period. Navitoclax was administered at 3 dose levels (DLs) (25, 50, 100 mg) in subjects weighing ≥ 45 kg, and up to 2 dose levels (25, 50 mg) in subjects weighing < 45 kg. Subjects weighing ≥ 45 kg were the first subjects to enroll into the study. These subjects were enrolled at a navitoclax dose of 25 mg (DL1). After escalation proceeded to 50 mg (DL2) in the ≥ 45 kg weight group, enrollment of subjects weighing < 45 kg began at a navitoclax dose of 25 mg (DL2).

A safety expansion cohort of approximately 20 subjects was planned to assess safety, including count recovery and efficacy of a determined dosing schedule that was cleared. The safety expansion cohort explored a 21-day of 28-day dosing schedule of venetoclax with 50 mg navitoclax (25 mg for subjects < 45 kg), the dosing schedule determined by collective safety and efficacy data following the dose escalation portion of the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 70 subjects total (approximately 50 subjects in dose escalation portion; approximately 20 subjects in safety expansion cohort)

Analyzed: 69 subjects total (47 subjects in the dose escalation portion; 22 subjects in the safety expansion cohort)

Diagnosis and Main Criteria for Inclusion:

Key Inclusion Criteria

- Subjects had R/R ALL or R/R LL (refractory was defined as persistent disease after at least 2 courses of chemotherapy.).
  - Subjects with ALL with Philadelphia chromosome (Ph+) or with an Abelson murine leukemia class targetable fusion were eligible.
  - Subjects with LL had radiographic evidence of disease.
- Subjects were ≥ 4 years of age.
  - Subjects < 18 years of age who did not have a standard of care treatment option available
- Subjects weighed ≥ 20 kg.
- Subjects were able to swallow pills.
- Subjects had adequate hepatic function:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × upper limit of normal (ULN) and bilirubin ≤ 1.5 × ULN (if subject received inotuzumab > 30 days prior to Day 1, had ALT, AST, and bilirubin < ULN),
  - Subjects with documented Gilbert's Syndrome may have had total bilirubin up to 4 × ULN but had a direct bilirubin of ≤ 1.5 × ULN.

Diagnosis and Main Criteria for Inclusion (Continued):

- Subjects had international normalized ratio (INR) ≤ 1.5 × ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.
- Subjects had normal creatinine for age or have a calculated creatinine clearance ≥ 60 mL/min/1.73 m^2.
- Subjects had adequate performance status:
  - Subjects ≤ 16 years of age: Lansky ≥ 50,
  - Subjects > 16 years of age: Karnofsky ≥ 50 or Eastern Cooperative Oncology Group (ECOG) < 3.

Key Exclusion Criteria

- Subjects who had central nervous system disease with cranial involvement that required radiation.
- Subjects who were less than 100 days post-transplant, or > 100 days post-transplant with active graft-versus-host disease or were still continuing post-transplant immunosuppressant therapy within 7 days prior to the first dose of study drug.
- Subjects who had received any of the following prior to the first dose of study drug:
  - Inotuzumab within 30 days (if subject received inotuzumab > 30 days prior to Day 1, had ALT, AST and bilirubin < ULN),
  - a biologic agent (i.e., monoclonal antibodies) for anti-neoplastic intent within 30 days,
  - CAR-T infusion or other cellular therapy within 30 days,
  - any anti-cancer therapy including blinatumomab, chemotherapy, radiation therapy, targeted small molecule agents, or investigational agents within 14 days, or 5 half-lives, whichever was shorter,*
    - * Exceptions: Ph+ ALL subjects on tyrosine kinase inhibitors at Screening could enroll and remain on tyrosine kinase inhibitor therapy to control disease. Subjects on venetoclax at screening could enroll and remain on venetoclax.
  - steroid therapy for anti-neoplastic intent within 5 days,
  - hydroxyurea that was ongoing (hydroxyurea was permitted up to the first dose).
- Subjects who received any of the following prior to the first dose of study drug:
  - a strong or moderate cytochrome p450 3A (CYP3A) inhibitor or inducer within 7 days,
  - aspirin within 7 days, or 5 half-lives, whichever was longer,
  - an excluded antiplatelet/anticoagulant drug or an herbal supplement that affects platelet function within 7 days, or 5 half-lives, whichever was longer,
- Subjects who consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the first dose of study drug.
- Subjects who had active, uncontrolled infection.
- Subjects who had not recovered to less than Common Terminology Criteria for Adverse Events Grade 2 from clinically significant adverse effect(s)/toxicity(s) of the previous therapy.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Venetoclax was administered as an oral tablet at doses of up to 400 mg (daily) during the study, and navitoclax was administered as an oral tablet at doses of up to 100 mg (daily) during the study. The following batches were supplied for the study:

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Venetoclax	Oral tablet	10 mg tablet	AbbVie	1000220684, 16-002361
Venetoclax	Oral tablet	50 mg tablet	AbbVie	1000220683, 16-005998
Venetoclax	Oral tablet	100 mg tablet	AbbVie	1000231738, 16-003565
Navitoclax	Oral tablet	25 mg tablet	AbbVie	15-001460

Duration of Treatment:

Subjects received study drug up to 9 months from the start of treatment.

Criteria for Evaluation

Efficacy:

The following efficacy evaluations were collected during the study: overall response rate (ORR), rates of complete response (CR), complete response with incomplete marrow recovery (CR_i), complete response without platelet recovery (CR_p), partial response (PR), progression-free survival (PFS), overall survival (OS), and minimal residual disease (MRD). Tumor assessments consisted of bone marrow aspiration with morphological or flow cytometry analysis (for ALL subjects or LL subjects with bone marrow involvement), lab collection, physical exam, and when clinically indicated, bone marrow biopsy, and radiographic imaging, if appropriate (computed tomography scan, magnetic resonance imaging, or positron emission tomography). Tumor assessments for LL subjects required radiographic imaging. Minimal residual disease assessment in peripheral blood and/or bone marrow was performed by local laboratories on available samples at times of disease assessment, if clinically indicated.

Pharmacokinetic:

Plasma concentrations of venetoclax and navitoclax were determined using a validated liquid/liquid extraction followed by high performance liquid chromatography with tandem mass spectrometric detection. The lower limit of quantitation (LLOQ) and upper limit of quantitation (ULOQ) for venetoclax were established at 2.12 ng/mL and 2030 ng/mL, respectively. The LLOQ and ULOQ for venetoclax in cerebral spinal fluid were established at 0.1 ng/mL and 25 ng/mL, respectively. The LLOQ and ULOQ for navitoclax were established at 5.07 ng/mL and 5070 ng/mL, respectively. Samples quantified below the lowest standard were reported as zero.

Values for the PK parameters of venetoclax and navitoclax including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) from time zero to 8 hours (AUC_8), the AUC from time zero to 24 hours (AUC_{24}), and apparent clearance (CL/F, CLFO) were determined using non-compartmental methods. For venetoclax and navitoclax, dose-normalized C_{max} and AUC values were calculated by dividing each of these PK parameters by the administered dose.

Criteria for Evaluation (Continued)

Safety:

The following safety evaluations were performed during the study: monitoring of adverse events (AEs) and assessments of laboratory tests.

Statistical Methods

Efficacy:

Efficacy analyses were completed with all treated subjects. The proportion of subjects with ORR (CR + CR_i + CR_p) for ALL and (CR + PR) for LL was calculated. Minimal residual disease in the peripheral blood and/or bone marrow was evaluated. Overall survival was analyzed by Kaplan-Meier methodology. Median OS was calculated, and the 95% confidence interval for median OS is presented. Progression-free survival was analyzed by Kaplan-Meier methodology. Median PFS was calculated, and the 95% confidence interval for median PFS is presented.

Pharmacokinetic:

Plasma concentrations and PK parameter values for venetoclax and navitoclax were tabulated for each subject and each dose combination. Summary statistics were computed for each sampling time and each PK parameter.

Safety:

For safety analyses, descriptive statistics are provided. Adverse events and laboratory evaluation changes were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events. Analyses of AEs included only treatment-emergent events (i.e., those that had an onset on or after the day of the first dose of study drug and no more than 30 days after the last dose of study drug). Dose-limiting toxicities were evaluated among subjects who had AEs meeting the DLT criteria. Laboratory measurements were explored for trends with dose and time and summarized by dose group and overall.

Summary/Conclusions

Efficacy Results:

The efficacy results from this study are as follows:

- Across all treated subjects, the ORR and CR rates were 66.7% and 56.5%, respectively, with an estimated median duration of response and duration of complete response of 3.8 and 6.5 months, respectively.
- The median OS was 6.6 months, and the median PFS was 3.0 months.
- Approximately 18.8% of subjects received subsequent SCT and 7.2% received subsequent CAR-T therapy.
- Across all subjects, exploratory analyses of MRD status revealed a bone marrow MRD negativity rate of 11.6%. The MRD negativity rate among subjects achieving CR/CR_i/CR_p was 20.5%.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

- Examination of efficacy parameters in subgroups of subjects based on age, disease, and dose level revealed differences between subgroups:
  - Age: Although the rates of response were generally high and duration of response and duration of complete response were similar between pediatric and adult subjects, the duration of OS was higher among pediatric subjects, and the duration of PFS was higher among adult subjects. In addition, the percentage of subjects proceeding to subsequent SCT or CAR-T therapy and achieving MRD negativity was higher for pediatric than adult subjects.
  - Disease: For all efficacy parameters assessed, efficacy was greater among subjects with B cell acute lymphoblastic leukemia (B-ALL) than among subjects with T cell acute lymphoblastic leukemia (T-ALL).
  - Dose level: The ORR, OS rate and duration, and PFS rate and duration were higher among subjects in DL1 and DL2 cohorts compared with DL3 or safety expansion cohorts. In addition, a greater proportion of subjects in DL2 than the other cohorts proceeded to subsequent SCT or CAR-T.
- Overall, the treatment regimen of venetoclax and navitoclax with chemotherapy showed evidence of anti-tumor activity in pediatric and adult subjects with R/R ALL or R/R LL.

Pharmacokinetic Results:

Venetoclax plasma concentrations peaked at approximately 6 to 8 hours (median T_{max}), and the mean ± standard deviation (SD) C_{max} and AUC_{24} for a 400 mg equivalent dose at steady state (Cycle 1 Day 8) were 1.92 ± 1.53 µg/mL and 30.0 ± 25.2 µg•h/mL, respectively. Pharmacokinetic exposures of 400 mg equivalent dose of venetoclax were comparable across different navitoclax dose levels and weight groups.

Navitoclax plasma concentrations peaked at approximately 6 to 8 hours (median T_{max}) across the 3 dose levels. The mean ± SD C_{max} values at steady state (Cycle 1 Day 8) for the 3 dose levels were 0.390 ± 0.244, 1.29 ± 0.971, and 1.95 ± 1.35 µg/mL, respectively, and the AUC_{24} values for the 3 dose levels were 5.92 ± 3.48, 19.9 ± 16.4, and 27.6 ± 17.1 µg•h/mL, respectively.

Summary/Conclusions

Safety Results:

The safety results from this study are as follows:

- The most commonly reported (≥ 40% of subjects) treatment-emergent adverse events (TEAEs) were hypokalemia, nausea, diarrhea, febrile neutropenia, abdominal pain, and vomiting.
- Overall, 97.1% of subjects reported Grade 3 or 4 TEAEs. The most commonly reported (> 20% of subjects overall) Grade 3 or 4 TEAEs were febrile neutropenia, neutropenia, anemia, hypokalemia, and ALT increased.
- Similar proportions of subjects had TEAEs that were considered by the investigator to have a reasonable possibility of being related to venetoclax or navitoclax (79.7% vs. 73.9%, respectively). The most commonly reported (> 20% of subjects overall) treatment-related events were anemia, neutropenia, febrile neutropenia, diarrhea, nausea, and vomiting.

Summary/Conclusions (Continued)

Safety Results (Continued):

- Forty-nine (71.0%) subjects died during the study, including 10 subjects with fatal TEAEs. Most fatal TEAE preferred terms were reported by single subjects, and 2 subjects had fatal TEAEs that were considered to have a reasonable possibility of being related to venetoclax or navitoclax. Most subject deaths (53.6%) were due to disease progression.
- A total of 52 (75.4%) subjects had at least 1 serious adverse event (SAE). The most commonly reported (> 5% of subjects) SAEs were febrile neutropenia, sepsis, septic shock, pneumonia, and upper respiratory tract infection.
- A total of 16 (23.2%) subjects had TEAEs leading to discontinuation of venetoclax or navitoclax. The most commonly reported (> 1 subject overall) events leading to discontinuation of study drug were febrile neutropenia, sepsis, and septic shock.
- The incidence rates of related TEAEs, Grade 3 or 4 TEAEs, SAEs, and AEs leading to discontinuation of study drug varied across cohorts, with no clear age- or dose-related trends.
- Dose-limiting toxicities were reported in 8 subjects in this study (5 adult subjects and 3 pediatric subjects). At DL1, for subjects ≥ 45 kg, 1 of 15 DLT-evaluable subjects had a DLT (neutropenia). At DL2, for subjects < 45 kg, 1 of 5 DLT-evaluable subjects had a DLT (neutrophil count decreased). At DL2, for subjects ≥ 45 kg, 1 of 5 DLT-evaluable subjects had 2 DLTs (blood bilirubin increased and drug-induced liver injury [DILI]). At DL3, for subjects < 45 kg, 2 of 4 DLT-evaluable subjects had DLTs (sepsis and delayed count recovery). At DL3, for subjects ≥ 45 kg, 3 of 9 DLT-evaluable subjects had DLTs (intestinal ischemia, pancytopenia, and blood bilirubin increased). Dose level 2 (25 mg for < 45 kg and 50 mg for ≥ 45 kg) was deemed by the Sponsor and principal investigators the maximally tolerated dose and the recommended dose for future studies. Based on these results, subjects in the safety expansion cohort received a 21-day of 28-day dosing schedule of venetoclax (400 mg adult equivalent dose) with 50 mg navitoclax (25 mg navitoclax for subjects < 45 kg).
- Overall, the combination of venetoclax and navitoclax was tolerated by pediatric and adult subjects with R/R ALL or R/R LL treated with or without chemotherapy. Safety data from this study are consistent with the previously demonstrated safety profile of venetoclax monotherapy and of navitoclax monotherapy. No new risks or increased severity in the identified risks of venetoclax or navitoclax were observed.

Summary/Conclusions (Continued)

Conclusions:

Demographic characteristics were similar across primary disease types, dose escalation cohorts, and the safety expansion cohort. The median duration of exposure to venetoclax was 45.0 days (range 1.0 to 597.0 days). The overall median duration of exposure to navitoclax was 39.0 days (range 5.0 to 595.0 days).

The treatment regimen of venetoclax and navitoclax with chemotherapy showed evidence of anti-tumor activity in pediatric and adult subjects with R/R ALL or R/R LL as evidenced by an ORR of 66.7% and CR rate of 56.5% with an estimated median OS of 6.6 months.

Venetoclax PK were not affected by coadministration of navitoclax. Venetoclax exposures were comparable across different navitoclax dose levels and weight groups.

Overall, the combination of venetoclax and navitoclax with chemotherapy was tolerated in both pediatric and adult subjects with R/R ALL or R/R LL. Based on the DLTs observed, the recommended doses were 25 mg of navitoclax for subjects < 45 kg and 50 mg for subjects ≥ 45 kg in combination with an adult equivalent of 400 mg of venetoclax in combination with chemotherapy. The safety events reported were consistent with the established safety profile of venetoclax and navitoclax.