

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Venetoclax, ABT-199, GDC-0199	Volume:	
Name of Active Ingredient: Venetoclax	Page:	
Title of Study: A Phase 2 Study of ABT-199 in Subjects with Acute Myelogenous Leukemia (AML)		
Coordinating Investigator: Marina Konopleva, MD		
Study Sites: 4 sites in the United States (US)		
Publications: 1 abstract		
Studied Period (Years): First Subject First Visit: 18 November 2013 Last Subject Last Visit: 19 December 2014	Phase of Development: 2	
Objectives: The primary objective was to evaluate the preliminary efficacy of venetoclax administered orally in patients with relapsed and/or refractory (R/R) AML or frontline in patients with AML who were unfit for intensive therapy. The secondary objective was to evaluate the preliminary safety of venetoclax administered orally in patients with AML. In addition, exploratory research to find biomarkers that may serve as surrogates for clinical endpoints in future venetoclax studies or to identify biomarkers or pharmacokinetic (PK) parameters that may be predictive of venetoclax activity were to be conducted.		
Methodology: Study M14-212 was a Phase 2, open-label, multicenter study evaluating the preliminary efficacy and safety of venetoclax administered orally in patients with AML. The study was to consist of 2 distinct portions. The first portion of the study was to consist of 19 subjects with the objective of evaluating anti-tumor effects and confirming the safety of the regimen. The second portion (expansion) was to consist of 35 additional subjects to evaluate anti-tumor effects and safety and was to commence if an adequate efficacy signal (i.e., $\geq 5/19$ achieved complete remission [CR], CR with incomplete blood count recovery [CRi] or partial remission [PR]) had been observed in the first portion of the study. The criterion for success would have been met if ≥ 16 of 54 subjects achieved remission. All efforts were made to adhere to these specified enrollment numbers, however, recognizing the acute nature of the disease, it was not possible to deny treatment to patients in screening for ethical reasons. The second portion of the study was not initiated because the results of the interim analysis deemed the efficacy signal from the first portion of the study to be insufficient. Post-treatment and survival information (i.e., the date and cause of death, post-treatment cancer therapies including transplantation, etc.) were to be collected (e.g., via telephone calls and/or clinical visits) at monthly intervals after the last study visit for a period of 2 years after the last subject had enrolled in the study.		

Number of Subjects (Planned and Analyzed): Part 1: 19 planned, 32 enrolled, 32 analyzed
Part 2 (expansion): 35 planned, 0 enrolled

Diagnosis and Main Criteria for Inclusion:

Subjects had to be ≥ 18 years of age with histological or cytological confirmation of relapsed or refractory AML (by World Health Organization [WHO] classification) OR untreated AML in patients who are unfit for intensive therapy. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and have adequate renal and liver function. Subjects were not eligible if they had a white blood cell count $> 25 \times 10^9/L$ and/or acute promyelocytic leukemia (French-American-British Class M3 AML).

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

Venetoclax was self-administered orally (PO) once daily (QD) within 30 minutes after the completion of breakfast or the subject's first meal of the day. All subjects were assigned a final target dose of 800 mg. Dosing began 20, 50, 100, 200, and 400 mg on Days 1, 2, 3, 4, and 5, respectively, and then 800 mg QD thereafter. Modifications to the regimen were permitted to respond to signals consistent with antitumor activity/tumor lysis.

Study Drug	Formulation	Route of Administration	Manufacturer	Bulk Lot Numbers
Venetoclax	10 mg tablet	Oral	Abbott/AbbVie	13-000449
Venetoclax	50 mg tablet	Oral	Abbott/AbbVie	13-000450
Venetoclax	100 mg tablet	Oral	Abbott/AbbVie	13-002285, 13-000452, 13-005759

Duration of Treatment:

Subjects continued venetoclax treatment until disease progression, withdrawal of consent, or other criteria for discontinuation were met (e.g., contraindicated treatment, toxicities requiring 3-week interruption, more than 2 dose reductions in the absence of clinical benefit, noncompliance).

Criteria for Evaluation

Efficacy:

A bone marrow aspiration and/or biopsy was conducted at Screening, after the first 4 weeks, and then every 8 weeks thereafter. Based on these results, all treated subjects were assessed per the International Working Group (IWG) criteria for AML at each post-baseline visit by the investigators.

- Complete Remission (CR): peripheral neutrophils at least $10^3/\mu L$, platelets $\geq 10^5/\mu L$ and bone marrow with $\leq 5\%$ blasts.
- CR with incomplete blood count recovery (CRi): bone marrow with $< 5\%$ blasts, with peripheral neutrophils of at least $10^3/\mu L$ or platelets $\geq 10^5/\mu L$.
- Partial Remission (PR): normalization in peripheral blood neutrophil and platelet counts with at least a 50% decrease in blasts persisting in bone marrow versus baseline.

Subjects who did not achieve CR, CRi or PR, and who did not exhibit clinical or cytological progressive disease (PD) per investigator discretion were considered to have stable disease (SD).

Criteria for Evaluation (Continued)

Pharmacokinetic:

Venetoclax PK samples were collected at 8 hours postdose on the day of the first dose and the first day of each new escalated dose for all subjects. Intensive PK samples (0 – 8 hour) were collected for venetoclax on Week 6 Day 1. For the intensive PK days, values for the PK parameters of venetoclax, 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) over an 8-hour and 24-hour dose interval (AUC_{0-8} and AUC_{0-24} , respectively) were determined using noncompartmental methods.

Safety:

Adverse event monitoring, vital signs, physical examination, electrocardiogram (ECG), and laboratory assessments were performed. Guidelines for tumor lysis syndrome (TLS) management were provided. All patients were hospitalized for the first week of dosing (during the escalation scheme from 20 to 800 mg).

Statistical Methods

Efficacy:

The primary efficacy endpoint was the proportion of subjects who achieved remission (i.e., CR, CRi or PR) based on the IWG criteria for AML, using a Simon 2-stage optimal design. Analyses of objective remission rate (ORR) as defined by CR + CRi + PR, CR rate, CRi rate, CR + CRi rate, duration of remission (DOR), time to progression (TTP), progression-free survival (PFS) overall survival (OS), the number of subjects who achieve minimal residual disease (MRD) negativity and the number of subjects who underwent subsequent transplant were performed for dosed subjects.

Pharmacokinetic:

Plasma concentrations of venetoclax, and PK parameter values were tabulated for each subject and each dose level by visit, and summary statistics were computed for each sampling time and each PK parameter.

Safety:

Safety analyses were performed for all dosed subjects. For the study as a whole, adverse events were evaluated and summarized. Laboratory test results and vital signs were explored for trends and summarized as appropriate.

Summary/Conclusions

The study population comprised 32 subjects with AML (30 previously treated, 2 previously untreated), including 13 subjects with secondary AML from antecedent hematologic disorder (myelodysplastic syndrome for 11 subjects and myeloproliferative neoplasms for 2 subjects). The subjects ranged from 19 to 84 years of age (mean: 65.9 years), and included 16 males and 16 females. All 32 subjects dose escalated to 800 mg QD, and 15 of these subjects further dose escalated to 1200 mg QD. The subjects received venetoclax for a mean of 80 days (range: 13 – 244 days).

Summary/Conclusions (Continued)

Efficacy Results:

The primary efficacy endpoint was the proportion of subjects who achieve remission (i.e., CR, CRi or PR) based on the IWG criteria for AML, using a Simon 2-stage optimal design, and the trial was to be considered successful if at least 16 of 54 subjects enrolled had achieved remission.

Based on a preplanned interim analysis, the efficacy signal from first portion of the study was deemed insufficient for enrollment into the second portion of the study, as 4 of the 19 subjects achieved CR/CRi. However, all subjects who were already in screening for study participation at the time of the interim analysis were allowed to initiate venetoclax treatment, and therefore, a total of 32 subjects were treated.

Overall, 6 of the 32 subjects (18.8%) achieved remission (2 CR, 4 CRi), and all 6 subjects had R/R disease, demonstrating activity of venetoclax as a single agent in AML. Five of the 6 subjects achieved remission within the first 5 weeks of treatment. Anti-leukemic activity was observed in 7 additional subjects (22%) with 50% bone marrow blast reduction, and evidence of hematopoietic recovery that included transfusion independence in 3 of these subjects with 2 cell line recoveries, and 1 cell line recovery in 1 of these subjects.

The DOR was not calculated because of the low remission rate. The median TTP was 2.5 months, and median PFS was 2.3 months (includes disease progression for 29 subjects and deaths for 2 subjects). The median OS was 4.7 months, with deaths reported for 27 of the 32 subjects. Minimal residual disease negativity was reported in 43.5% (10/23) of subjects. Five of the subjects with an objective remission were MRD negative and 1 subject remained MRD positive. One of the 32 subjects with R/R AML who had evidence of blast reduction had subsequent stem cell transplant.

Pharmacokinetic Results:

Following multiple-dose administrations of 800 mg venetoclax in 13 subjects with AML, the median time to reach peak plasma concentrations was 6 hours, and the mean C_{max} and AUC_{0-24} were 3.74 $\mu\text{g/mL}$ and 61.6 $\mu\text{g}\cdot\text{h/mL}$, respectively.

Safety Results:

All 32 subjects (100%) treated with venetoclax each experienced at least 1 TEAE. Treatment-emergent adverse events, regardless of severity or relationship to venetoclax, reported in $\geq 30\%$ of subjects were nausea (59.4%), diarrhea (56.3%), vomiting (40.6%), hypokalemia (40.6%), fatigue (34.4%), hypomagnesemia (34.4%), headache (34.4%), febrile neutropenia (31.3%), and hypophosphatemia (31.3%). Adverse events rated as NCI CTC grade 3 or 4 were reported in 81.3% (26/32) of subjects. The most common ($\geq 10\%$) grade 3 or 4 TEAEs were febrile neutropenia (31.3%), hypokalemia (21.9%), pneumonia (18.8%), urinary tract infection (12.5%), and hypotension (12.5%).

The investigator assessed TEAEs as having a reasonable possibility of being related to venetoclax for 75% of subjects (24/32). Treatment-emergent adverse events with a reasonable possibility of being related to venetoclax and reported in at least 10% of subjects were nausea (40.6%), diarrhea (25.0%), vomiting (15.6%), and fatigue (15.6%).

Treatment-emergent adverse events led to death in 37.5% (12/32) of subjects, and included 10 deaths due to disease progression and 2 deaths due to other causes (Crohn's disease and pneumonia). All deaths were assessed by the investigator as having no reasonable possibility of being related to venetoclax.

Summary/Conclusions (Continued)

Safety Results (Continued):

Serious TEAEs, including deaths, occurred in 84.4% (27/32) of subjects. Serious adverse events reported in $\geq 10\%$ of subjects were febrile neutropenia (28.1%), malignant neoplasm progression (25.0%), and pneumonia (15.6%). The serious adverse events were assessed as having a reasonable possibility of being related to venetoclax in 3 subjects (pseudomonal bacteremia in 1 subject, febrile neutropenia in 1 subject, and diarrhea in 1 subject).

Adverse events led to discontinuation of venetoclax in 31.3% (10/32) of subjects. Of the 10 subjects who discontinued because of TEAEs, 7 discontinued because of adverse events related to disease progression, 2 discontinued because adverse events not related to disease progression (fatal Crohn's disease for 1 subject; febrile neutropenia, dyspnea, and cough for 1 subject), and 1 discontinued because of both an adverse event related to disease progression (fatal malignant neoplasm progression) and an adverse event not related to disease progression (purpura).

Treatment-emergent adverse events that led to an interruption in venetoclax dosing for more than 1 subject were febrile neutropenia (n = 2) and diarrhea (n = 2). No TEAEs led to a venetoclax dose reduction.

Treatment-emergent adverse events identified using the neutropenia search criteria were reported in 31.3% (10/32) of subjects. The neutropenia events were serious for 9 of the 10 subjects, and concurrent with infections for 7 of the 10 subjects (pneumonia in 5 subjects, lung infection in 1 subject, and candida infection [oral] in 1 subject). Eight of these 10 subjects had grade 3 or 4 decreased neutrophil counts on Day 1.

No cases of TLS concurrent with venetoclax were reported.

Decreases in neutrophil count were observed that were not progressive over time. Although over 50% of subjects had laboratory values that shifted from grade 0 – 2 at baseline to grade 3 or 4 during the study for neutrophils (100%), platelet count (100%), WBC count (77.3%), and hemoglobin (69.2%), few subjects had hematology results reported as grade 3 or 4 adverse events (31.3% for febrile neutropenia, 9.4% for anemia, 6.3% for WBC count decreased, 3.1% for pancytopenia, 3.1% for neutrophil count decreased, and 3.1% for platelet count decreased).

No clinically meaningful observations were noted for clinical chemistry, vital signs, or ECG assessments.

Conclusions:

Venetoclax at 800 mg once daily has an acceptable safety profile in patients with R/R AML and those unfit for intense chemotherapy. No new safety signals were identified compared to venetoclax monotherapy trials in other hematologic malignancies. Although TLS was identified as a risk with venetoclax treatment in subjects with chronic lymphocytic leukemia (CLL), subjects in this study received prophylaxis for TLS during dose escalation and no cases of TLS were observed during venetoclax treatment.

Summary/Conclusions (Continued)

Conclusions:

Salvage treatment with intensive regimens in R/R AML aim at achieving a complete remission to enable subsequent allogeneic hematopoietic-cell transplantation. The only treatment options for patients who are physically unfit to receive intensive salvage therapy or have exhausted conventional regimens are best supportive care or investigational agents in clinical trials. Many of the subjects enrolled in to this study had secondary AML and had failed standard induction therapy, and/or stem cell transplant, as well as less intense therapy with hypomethylating agents including decitabine and azacitidine. This study confirmed pre-clinical activity of venetoclax as monotherapy evidenced by rapid objective responses and stabilization of disease in these heavily pre-treated AML subjects with poor prognostic features and limited treatment options.