SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development, Unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	Not applicable
Name of Active Ingredient(s)	JNJ-26481585

Protocol No.: 26481585CAN1003

Title of Study: A Phase 1 Study of the Histone-Deacetylase Inhibitor JNJ-26481585 in Subjects with Advanced or Refractory Leukemia or Myelodysplastic Syndrome

NCT No.: NCT00676728

Clinical Registry No.: CR013960

Principal Investigator(s): Guillermo Garcia Manero, M.D. (The University of Texas MD Anderson Cancer Center, Houston, TX; USA)

Study Center(s): The study was carried out in 2 centers in the United States of America.

Publication (Reference): None.

Study Period: 2 March 2009 to 3 August 2010.

Phase of Development: Phase 1.

Objectives: The primary objective of the study was to determine the safety profile (adverse event [AE] profile, dose-limiting toxicity [DLT], and maximum tolerated dose [MTD]) of JNJ-26481585.

The secondary objectives of the study were: to determine the pharmacokinetic profile of JNJ-26481585, to explore the pharmacodynamic effects of JNJ-26481585, and to explore antitumor activity of JNJ-26481585.

Methodology: This was a 2-part open-label, Phase 1 dose escalation study to explore the safety, pharmacokinetics, pharmacodynamics, and the activity of JNJ-26481585 in subjects with advanced or refractory leukemia or myelodysplastic syndrome (MDS). In Part I of the study, the MTD was to be determined using rapid escalation followed by conventional escalation of dose. Decisions on dose escalation or de-escalation, changes in the timing of pharmacokinetic/pharmacodynamic sampling, and the exploration of an alternative schedule were to be made by the Study Evaluation Team (SET), which consisted of all principal investigators, the medical monitor, and 1 of the sponsor's clinical pharmacologists. Part II of the study was the expansion phase, which was to begin after the MTD had been determined. The starting dose for subjects enrolled in Part II of the study was to be the MTD established in Part I.

Number of Subjects (planned and analyzed): The planned sample size for Parts I and II was 27 to 72 subjects. Twenty-three subjects were screened and 10 subjects received at least 1 dose of JNJ-26481585, 5 subjects at the 4-mg dose and 5 subjects at the 6-mg dose. All subjects who received at least 1 dose of study treatment were analyzed for efficacy and safety. Treatment in the study was stopped early because of enrollment and recruitment issues.

Diagnosis and Main Criteria for Inclusion: Male or female adult subjects with advanced or refractory leukemia or MDS, not amenable to other available standard treatment options were allowed in this study. All subjects were to have adequate cardiovascular, renal, and hepatic function as defined in the protocol (appendix 1). Key exclusion criteria included known or suspected involvement of the central nervous system, recent antitumor therapy, and presence of cardiovascular risk factors.

Test Product, Dose, and Mode of Administration, Batch No.: JNJ-26481585, administered orally starting at 4 mg daily. Batch numbers: 360130, 360131, 362774, 362470, 362469, and 362775.

Duration of Treatment: Subjects were treated until progression or unacceptable toxicity. The duration of treatment for the 10 subjects ranged from 1 cycle to 21 cycles.

Criteria for Evaluation: The anticancer activity of JNJ-26481585 was explored by assessment of response as defined by current response guidelines for acute myeloid leukemia (AML), acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, or MDS. The main parameters of response assessment included complete blood count, transfusion requirements, bone marrow aspirate/biopsy, and tumor assessment by radiographic studies or by physical examinations.

Venous blood samples (during Part I and Part II) and urine samples (during Part I only) for determination of plasma concentrations of JNJ-26481585 and the acid metabolite (JNJ-26395018) were collected at time points specified in the Time and Events Schedule in the protocol.

Venous blood samples and bone marrow samples were collected at the time points specified in the Time and Events Schedule in the protocol to assess biomarkers for pharmacodynamic effects. These pharmacodynamic markers included, but were not limited to, histone acetylation, heat shock protein 90 acetylation downstream effects, and interleukin 6. Additional molecular characterization of biopsies (such as immunohistochemistry, real-time quantitative polymerase chain reaction, DNA microarray) was to be carried out depending on tissue quality and homogeneity.

A pharmacogenomic blood sample was to be collected to allow for pharmacogenomic research, as necessary (where local regulations permit).

Safety evaluations included an assessment of AEs, clinical laboratory data, electrocardiograms (ECGs), Multiple Gated Acquisition (MUGA) scan or echocardiography, Holter monitor, vital signs measurements, physical examination findings, and Eastern Cooperative Oncology Groups (ECOG) performance status.

Statistical Methods: No formal power calculations were performed to predetermine sample size. The number of subjects needed (27 to 72) to complete the study was based upon clinical and statistical judgment and was to depend on the dose level at which the MTD was observed. All efficacy and pharmacodynamic measures were listed, tabulated, and, where appropriate, plotted. Subjects were grouped by prescribed dose and dosing schedule, as appropriate for summarizing the data. No statistical inference was made.

The pharmacokinetic parameters were summarized by means of descriptive statistics by dosing schedule. Derived pharmacokinetic parameters were presented graphically, as appropriate.

RESULTS:

STUDY POPULATION: The study population evaluated for safety and efficacy comprised all subjects who received at least 1 dose of JNJ-26481585. Twenty-three subjects were screened, and of those subjects, 10 received JNJ-26481585; 5 subjects received 4-mg, and 5 subjects received 6-mg. Six subjects completed treatment cycle 1 (3 from each cohort). The most common reason for study withdrawal was progressive disease (4 subjects), followed by AEs (3 subjects), lack of efficacy and “other” (1 subject each). At the time of database lock, 1 subject remained in the study receiving 6-mg JNJ-26481585.

The median age was 63 years (range: 54 to 81 years). At study entry, 5 subjects had MDS, and 5 subjects had AML.

EFFICACY RESULTS: Disease progression was observed for 4 subjects, 3 subjects from the 4-mg cohort and 1 subject from the 6-mg cohort. The time to disease progression in these 4 subjects ranged from 10 to 87 days. One subject with MDS demonstrated a significant reduction in transfusion dependency on study drug at the 6-mg dose level and continued treatment at the time of completion of this report.

PHARMACOKINETIC RESULTS: After single- and multiple-dose administration, the peak concentration and total exposure (AUC_{last}) of both JNJ-26481585 and its metabolite (JNJ-26395018) appeared to be within the same range for the 4- and 6-mg dose cohorts. The time to reach maximum plasma concentrations was similar in the 2 dose cohorts. No apparent accumulation after multiple administrations could be observed.

The observed plasma concentration of the metabolite (JNJ-26395018) was higher than the parent compound (JNJ-26481585).

SAFETY RESULTS: Nine of the 10 subjects in the study experienced 1 or more AE. Four subjects (2 in each cohort) experienced AEs considered by the investigator to be related to the study drug. By preferred term, drug-related AEs experienced by more than 1 subject were cardiac disorder (QTcF prolongation; 3 subjects) and diarrhea (2 subjects).

No subjects died during the study. Three subjects experienced serious adverse events (SAEs); 1 subject in the 4-mg dose cohort (hypoxia, leukocytosis, and pyrexia, all considered by the Investigator as not related to study drug) and 2 subjects in the 6-mg dose cohort (pneumonia, considered by the Investigator as not related to study drug, and atrial fibrillation, considered by the Investigator as possibly related to study drug). There were no DLTs reported.

Four subjects discontinued study drug because of AEs; 1 subject in the 4-mg dose cohort (hypoxia, leukocytosis, and pyrexia, all considered by the Investigator as not related to study drug) and 3 subjects in the 6-mg dose cohort (ventricular tachycardia, not related to study drug; cardiac disorder [QTcF prolongation], considered possibly related; and atrial fibrillation, considered possibly related).

STUDY LIMITATIONS: Enrollment in the study was stopped early because of recruitment issues.

CONCLUSION(S): This Phase I dose escalation study was conducted in subjects with relapsed or refractory leukemia or MDS. The study was discontinued after completion of 2 dose levels (4 mg and 6 mg daily) and no MTD was determined. The reason for discontinuation of the study was poor recruitment.

For the pharmacokinetic analyses, limited data were available, the sample size was small and the intersubject variability was high; however, the analysis outcome indicates that after single- and multiple dose administration, the kinetics of JNJ-26481585 is characterized by a rapid absorption and a biphasic decline. After single- and multiple-dose administration, the peak concentration and total exposure (AUC_{last}) of JNJ-2481585 and its metabolite (JNJ-26395018) appeared to be within the same range for the 4- and 6-mg dose groups. The time to reach maximum plasma concentrations was comparable. No clear accumulation after multiple administrations could be observed. All pharmacodynamic data is supplied in a separate report.

In each dose level cohort, 5 subjects were enrolled, of whom, 3 subjects in each cohort were evaluable for toxicity. No DLTs have been observed in this study. The most commonly reported drug-related AEs were cardiac disorder (QTcF prolongation; 3 subjects, all Grade 2 as per Central Reader) and diarrhea (2 subjects). One subject reported Grade 3 asthenia on study treatment at the 4-mg dose level. Cardiovascular AEs considered related to study drug were observed in 3 subjects: Grade 2 cardiac

disorder (QTcF prolongation) in 1 subject in the 4-mg cohort; Grade 3 cardiac disorder (QTcF prolongation) in 1 subject in the 6-mg cohort (confirmed by Central Reader as Grade 2 QTcF prolongation); and Grade 2 cardiac disorder (QTcF prolongation), Grade 2 non-sustained ventricular tachycardia (NSVT), and Grade 3 atrial fibrillation in 1 subject in the 6-mg cohort.

No subject died during the study. Three subjects experienced SAEs; 1 SAE was considered possibly drug-related (atrial fibrillation at the 6-mg dose level).

One subject with MDS in the 6-mg cohort had evidence of clinical benefit with a significant reduction in transfusion dependency on study drug. This subject continued in the study at the time of completion of this study report. All other subjects were discontinued for lack of efficacy (1 subject), progressive disease (4 subjects), AEs (3 subjects), or subject choice (1 subject).

Adverse events leading to discontinuation of study drug included hypoxia, leukocytosis, and pyrexia in 1 subject in the 4-mg cohort (considered by the investigator as not related to study drug), NSVT in 1 subject in the 6-mg cohort (considered by the investigator as not related), cardiac disorder (QTcF prolongation) in 1 subject in the 6-mg cohort (considered by the investigator as possibly related), and atrial fibrillation in 1 subject in the 6-mg cohort (considered by the investigator as possibly related).

Overall, the safety profile observed in this study is similar to that observed in an ongoing study with JNJ-26481585 in subjects with solid malignancies and lymphoma, and comparable to what has been observed with other HDAC inhibitors in clinical development or marketed.