SYNOPSIS

Name of Sponsor/Company	Xian Janssen Pharmaceutical Ltd.
Name of Investigational Product	JNJ-16269994-AAA (Itraconazole)

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Prepared by: Xian Janssen Pharmaceutical Ltd.

Protocol No.: R051211FUN4057

Title of Study: A Multicenter, Randomized Trial Comparing The Efficacy of Intravenous Followed by Oral Itraconazole With Intravenous Caspofungin For Empiric Antifungal Therapy in Neutropenic Subjects With Hematological Malignancy

NCT No.: NCT02895529

Clinical Registry No.: CR108202

Principal Investigator: Huang Xiaojun, MD, Peking University People's Hospital, [redacted], China

Study Center(s): 13 sites in China

Publication (Reference): None

Study Period: 20 December 2016 (Date first subject signed informed consent) to 02 May 2018 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 4

Objectives: The primary objective of the study was to investigate the hypothesis that the efficacy of intravenous (IV) itraconazole followed by oral itraconazole was non-inferior to that of IV caspofungin as empiric therapy for suspected fungal infection subjects with fever and neutropenia. The secondary objective of the study was to evaluate the response rate of each individual endpoint of efficacy and describe the safety of itraconazole (IV administration followed by oral administration or IV administration alone) compared to caspofungin (IV regimen) in suspected fungal infection subjects with fever and neutropenia.

Methodology: This was a Phase 4, randomized, open-label, active-controlled, multicenter, interventional, 2-arm study to assess the efficacy and describe the safety of itraconazole (IV followed by oral formulation) compared to caspofungin (IV regimen) as empiric therapy in suspected fungal infection subjects with fever and neutropenia. Subjects eligible for this study were men or women 18 years of age or older with a diagnosis of suspected fungal infection presenting with persistent fever and neutropenia combined with hematological disease. Subjects were randomly assigned in a 2:1 ratio to receive itraconazole or caspofungin in this study. Randomization was stratified by degree of risk (whether subjects have received allogeneic hematopoietic stem cell transplantation [HSCT] or chemotherapy for acute leukemia relapse or abnormal radiological data) and previous use of systemic antifungal prophylaxis therapy (yes or no).

Number of Subjects (planned and analyzed): Subjects planned: 408 subjects. Subjects randomized (modified intent-to-treat [mITT]/per protocol [PPS]): 61 subjects (39 subjects: Itraconazole; 22 subjects: Caspofungin). Safety population: 61 subjects (39 subjects: Itraconazole; 22 subjects: Caspofungin).

Diagnosis and Main Criteria for Inclusion: The study population included adult hematologic malignancy subjects aged ≥18 years of age, with diagnosis of fever and neutropenia with neutrophil count <500/μL, and have met the inclusion/exclusion criteria for entry into the study. Potential subjects were excluded from participating in the study if they met any/all of the exclusion criteria, such as diagnosis of liver disease or renal insufficiency, or use of any prohibited medication outlined in the exclusion criteria.

Test Product, Dose and Mode of Administration, Batch No.: For the itraconazole group, subjects were received 200 mg of itraconazole IV twice daily on Day 1 and Day 2, followed by 200 mg once daily through Day 14; batch numbers: 16BQ102, 16KQ106, and 17EQ150. From Day 15 to Day 28, subjects were received 200 mg (20 mL) of itraconazole oral solution twice daily; batch numbers: FJB2H00, GAB5302, and HBB4I00. Subjects, who were not suitable for oral administration of itraconazole based on the investigator's judgment, received 200 mg of itraconazole IV once daily from Day 15 to Day 28. Each IV infusion was completed over 1 hour.

Reference Therapy, Dose and Mode of Administration, Batch No.: For the caspofungin group, subjects were received 70 mg of caspofungin IV once daily on Day 1, and 50 mg of caspofungin IV once daily thereafter through Day 28; batch numbers: 2206080, 2207910, M035322, and M023627. Each IV infusion was completed over 1 hour.

Duration of Treatment: The maximum duration of this study was 65 days, including a screening phase with a maximum duration of 7 days, a treatment phase with a maximum duration of 28 days and a 30-day post-treatment phase after the last dose of study drug.

Criteria for Evaluation: Efficacy analyses were conducted on the PPS. For sensitivity and supportive purposes, the efficacy analyses were repeated using mITT analysis set. Subgroup analyses of efficacy were provided on the subset of subjects who received OS as a sequential treatment in the itraconazole treatment group. Safety assessments included measurement of vital signs, physical examinations, review of concomitant therapy and procedures, and a review of AEs, serious adverse events (SAEs), and deaths. Laboratory testing was performed to identify abnormalities in blood chemistry, and hematologic parameters. Baseline electrocardiograms (ECGs) were performed.

Statistical Methods:

In this study, non-inferiority was defined as retaining 75% of the caspofungin treatment effect as measured by 5 composite endpoints. Assuming a response rate for the composite endpoints in caspofungin treatment was 40%, additional 3% response rate in favor of itraconazole under the alternative hypothesis, a 2:1 randomization ratio between 2 treatments (itraconazole and caspofungin), and a 1-sided significance level of 2.5%, with 366 subjects (244 in itraconazole and 122 in caspofungin), there was 80% power to demonstrate non-inferiority of itraconazole to caspofungin with a margin of 75% in the retention rate. With 10% is expected to be excluded from the PP set, 408 subjects (272 in itraconazole and 136 in caspofungin) would be randomized.

The primary efficacy endpoint was defined as the composite endpoints. The primary analysis was performed on the PPS (N=61). As a sensitivity analysis, the primary efficacy analysis also was performed on the mITT set (N=61). The major secondary endpoints were the individual items of the composite endpoints. Analysis was done as the primary endpoint. Adverse events, laboratory analyte values, vital sign measurements, 12-lead ECG data, and deaths reported during the study were to be summarized. Safety variables were tabulated by descriptive statistics using the safety population (N=61).

RESULTS:

STUDY POPULATION:

From 20 Dec 2016 until 02 May 2018, a total of 70 subjects were screened, 61 subjects were randomized in the study. All the randomized subjects comprised the mITT population, met the criteria of Per-protocol set (PPS), and were in the safety set (SS) as well. In this study, mITT, PPS and SS were with the same subjects. Sixteen (41%) subjects in the itraconazole group and 6 （27.3%） subjects in the caspofungin group discontinued treatment. Six (15.4%) subjects in the itraconazole group and 1 (4.5%) subjects in the caspofungin group discontinued due to lack of efficacy. Five (12.8%) subjects in the itraconazole group and 2 (9.1%) subjects in the caspofungin group discontinued due to withdrawal by subject. Treatment discontinuations due to non-compliance with study visit were reported in 2 (5.1%) subjects in the itraconazole group and no subject in the caspofungin group. One (2.6%) subject in the itraconazole group and 2 (9.1%) subjects in the caspofungin group discontinued due to TEAEs with an outcome death only; 2 and 0 subjects, respectively, discontinued due to TEAEs only.

With a few exceptions, demographics and disease characteristics were generally well balanced between the 2 treatment groups. All subjects were Asian. Half (50.8%) of the all treated subjects were male. The median age was 34 years in the itraconazole group and 47.5 years in the caspofungin group. Thirty-eight (97.4%) subjects in the itraconazole group were <65 years of age, compared with 21 (95.5%) subjects in the caspofungin group. At baseline, 87.2% of subjects in the itraconazole group were diagnosed leukemia, compared with 95.5% of subjects in the caspofungin Group; 5.1% versus 4.5% of subjects, respectively, were MDS/MPD; two (5.1%) and one (2.6%) subjects in the itraconazole group were diagnosed lymphoma and aplastic anemia, respectively.

EFFICACY RESULTS:

Due to the small sample size, treatment with itraconazole could not provide a significant non-inferiority conclusion by achieving a lower limit of 95% CI above 0.75. However, the point estimate is greater than 0.75. In this study, the subjects from the itraconazole group reached to the defervescence in a shorter time than caspofungin. Key efficacy results are as follows:

- For the primary efficacy analysis and subgroup analysis of primary endpoint:
  - The response rates of subjects who achieved all of 5 composite endpoints were 51.3% and 63.6% in the itraconazole group and caspofungin group, respectively. The RR (95% CI) of itraconazole group vs caspofungin group was 0.802 (0.515, 1.248) with the CMH method after adjusting stratification factors.
  - The response rates of the subgroup subjects who achieved all of 5 composite endpoints were 66.7% and 63.6% in the itraconazole subgroup and caspofungin group, respectively. The RR (95% CI) of itraconazole subgroup vs caspofungin group was 1.048 (0.599, 1.833).
- For the secondary efficacy analysis and subgroup analysis of secondary endpoint, each individual endpoint showed that there was no statistically significance between itraconazole and caspofungin treatment (P>0.05).
- The results of other efficacy analyses that measure the response rate and success rate also showed no statistically significance between the two groups. However, subjects from the itraconazole group reached to the defervescence in a shorter time than caspofungin. The result from a sensitivity analysis of time to defervescence with randomization factors as covariates in cox proportional hazards model was consistent with results from stratified model.

SAFETY RESULTS:

- Treatment emergent adverse events were reported in 76.9% of subjects in the itraconazole group versus 90.9% of subjects in the caspofungin group; Toxicity ≥Grade 3 TEAEs were reported in 48.7% of subjects in the itraconazole group versus 45.5% of subjects in the caspofungin group; serious TEAEs were reported in 17.9% versus 18.2% of subjects; TEAEs leading to study drug discontinuation were reported in 15.4% versus 9.1% of subjects; TEAEs leading to study discontinuation were reported in 5.1% versus 0% of subjects; infusion reaction TEAEs were reported in 5.1% versus 9.1% of subjects; infection TEAEs were reported in 30.8% versus 36.4% of subjects; and TEAEs with an outcome of death were reported in 7.7% versus 18.2% of subjects, respectively. The TEAEs in the two groups are almost comparable. Though differences of percentages of a few TEAEs between two treatment groups were observed, it is caused by the small TEAE frequency numbers. These differences could be assumed not to be significant when the enrolled subjects increased.

In subjects with OS itraconazole as sequential treatment, the number of subjects with TEAEs was 9 (100%), the number of subjects with Toxicity ≥Grade 3 TEAEs was 6 (66.7%), the number of subjects with serious TEAEs, TEAEs leading to study drug discontinuation, and infusion reaction TEAEs was 2 (22.2%; one occurred in the IV treatment phase and the other occurred in the 12 days after the OS), the number of subjects with infection TEAEs was 3 (33.3%), no subject with TEAE leading to death.

- The most common TEAEs by SOC and PT (reported in >10% in either in the itraconazole group or caspofungin group) were hypokalaemia (30.8% versus 31.8%), hypoalbuminaemia (20.5% versus 4.5%), pyrexia (17.9% versus 0%), alanine aminotransferase increased (15.4% versus 0%), lung infection (12.8% versus 9.1%), aspartate aminotransferase increased (12.8% versus 0%), rash (10.3% versus 13.6%), vomiting (10.3% versus 9.3%), upper respiratory tract infection (7.7% versus 13.6%), and blood lactate dehydrogenase increased (5.1% versus 13.6%). Though differences of percentages of a few TEAEs by SOC and PT between two treatment groups were observed, it is caused by the small TEAE frequency numbers. These differences could be assumed not to be significant when the enrolled subjects increased.

  — The most frequently reported TEAEs with Toxicity ≥Grade 3 (reported in >10% in either in the itraconazole group or caspofungin group) were lung infection (10.3% versus 4.5%) and hypokalaemia (7.7% versus 13.6%).

  — The most frequently reported serious TEAEs (reported in >5% in either in the itraconazole group or caspofungin group) were lung infection (5.1% versus 4.5%) and sepsis (5.1% versus 4.5%).

  — The most frequently reported TEAEs leading to study drug withdrawal (reported in >5% in either in the itraconazole group or caspofungin group) were lung infection (5.1% versus 0%) and vomiting (5.1% versus 0%).

  — The most frequently reported infection TEAEs (reported in >5% in either in the itraconazole group or caspofungin group) were lung infection (7.7% versus 9.1%), upper respiratory tract infection (5.1% versus 13.6%), pyrexia (7.7% versus 0%) and sepsis (5.1% versus 0%).

  — The most frequently reported drug related TEAEs (reported in >5% in either in the itraconazole group or caspofungin group) were alanine aminotransferase increased hypokalaemia (5.1% versus 4.5%), (5.1% versus 0%) and vomiting (5.1% versus 0%).

  — There were no TEAEs with an outcome of death, TEAEs leading to study discontinuation or infusion reaction TEAEs reported in >5% in either treatment group.

- A few changes of clinical laboratory evaluation between two treatment groups were different, but it is caused by the small TEAE frequency numbers. These differences could be assumed not to be significant when the enrolled subjects increased.
  - All subjects were in low neutrophils at baseline, but 34.7% of subjects in the itraconazole group and 57.1% of subjects in the caspofungin group were normal or high neutrophils after last dose.
  - Most subjects had low or normal ALT and AST at baseline and after treatment.
  - Most subjects were in abnormal high temperature at baseline, but the value is gradually descending to normal temperature after treatment.
  - With a few exceptions, microbiological culture of bacteria and fungal were generally negative in the 2 treatment groups.

CONCLUSION:

For men or women with a diagnosis of suspected fungal infection presenting with persistent fever and neutropenia combined with hematological disease, Study R051211FUN4057 establishes that treatment with itraconazole could not provide a significant non-inferiority conclusion. However, the point estimate is greater than 0.75. Each individual endpoint showed that there was no statistically significance between itraconazole and caspofungin treatment. The results of other efficacy analyses that measure the response rate and success rate also found no statistically significance between the two groups. But the subjects from the itraconazole group reached to the defervescence in a shorter time than caspofungin.

The TEAEs in the two groups are almost comparable. Though differences of percentages of a few TEAEs between two treatment groups were observed, it is caused by the small TEAE frequency numbers. These differences could be assumed not to be significant when the enrolled subjects increased.

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