Pharmacokinetics of Isavuconazole Administered as Isavuconazonium Sulfate Intravenous Solution via Nasogastric Tube or Orally in Healthy Volunteers

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ABSTRACT

Background: Nasogastric (NG) tube feeding is most common in the intensive care unit and is also used for cancer patients who are unable to eat (e.g. patients with mucositis) or do not want to eat due to severe nausea. For such critically ill patients with invasive fungal infections, administration of isavuconazonium sulfate (ISAVUSULF) via NG tube can be an alternate route of drug administration.

Methods: This was a randomized, open-label, 2-period, 2-sequence single dose crossover study in healthy male and female subjects. Each subject participated in 2 treatment periods separated by a washout of at least 30 days between investigational product administrations in each period. Subjects were administered a single dose of 372 mg ISAVUSULF intravenous (IV) solution via NG tube (test formulation) or 372 mg ISAVUSULF capsules for oral (PO) administration (i.e., PO capsules administered to subjects without NG tube) (reference formulation) under fasting conditions on day 1 of each period. Pharmacokinetic (PK) samples were collected predose on day 1 of each period and at multiple time points postdose through day 21. Standard safety and tolerability assessments were conducted in each period.

Results: Eighteen subjects were randomized in this study and 13 provided concentrations in both sequences that were PK evaluable. The analysis of variance estimate of the study population suggests that the isavuconazole IV NG tube administration geometric least-square (LS) mean values of the observed maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC) to the last measurable concentration (AUC_{last}), AUC to time infinity (AUC_{inf}), and AUC from start of dosing to 72 hours (AUC_{72}) were 106.1%, 97.7%, 99.3% and 98.1%, respectively, of the corresponding oral administration values. The geometric LS mean ratio and 90% Confidence Intervals for the C_{max}, AUC_{last}, AUC_{inf}, and AUC_{72} are completely contained within the prespecified limits of 80% to 125%. There were no deaths or serious adverse events that led to withdrawal of treatment during the conduct of the study.

Conclusion: The study met its primary endpoint of bioequivalence between the two routes of administration in this population. Both routes of administration are well tolerated.

BACKGROUND

- Isavuconazonium sulfate (ISAVUSULF), prodrug of active moiety isavuconazole (ISAV), has been approved as a broad-spectrum antifungal agent for the treatment of invasive aspergillosis and invasive mucormycosis[1]
- ISAV fills a substantial medical need for a well-tolerated, easily administered, broad spectrum antifungal agent for the treatment of invasive fungal infections[2]
- Nasogastric (NG) tube feeding is most common in the intensive care unit and is also used for cancer patients who are unable to eat (e.g. patients with mucositis) or do not want to eat due to severe nausea[3]
- Limited data regarding alternate routes of administration for ISAVUSULF and its pharmacokinetic (PK) properties are available[4]
- Primary objective:
  - To assess the bioequivalence of IV solution of ISAVUSULF via NG tube (test formulation) versus ISAVUSULF capsules for PO administration (i.e., oral capsules, reference formulation)
- Secondary objective:
  - To monitor the safety and tolerability of two single doses of ISAVUSULF, 30 days apart

METHODS

Study design

- Randomized, open-label, 2-period, 2-sequence single dose crossover study in healthy male and female subjects
- Subjects were randomized in 1:1 ratio to receive a single dose of 372 mg ISAVUSULF intravenous solution (IV) via NG tube (test formulation) or 372 mg (two 186 mg capsules) ISAVUSULF capsules for oral administration (PO: reference formulation) under fasting conditions on day 1 of each treatment period
- Both IV ISAVUSULF solution via NG tube (test formulation) and PO capsules were administered as a single oral dose under fasting conditions
- Washout of at least 30 days between study drug administration in each period
- Correct placement of the NG tube was confirmed using X-ray radiography
- ISAV PK samples were collected predose on day 1 and at the following postdose time points: 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 168, 240, 336 and 480 hours

Assessments

- Primary ISAV PK parameters assessed were: observed maximum plasma concentration (C_{max}), area under the plasma concentration–time curve (AUC) to the last measurable concentration (AUC_{last}), AUC to time infinity (AUC_{inf}), and AUC from start of dosing to 72 hours (AUC_{72})
- Clinical laboratory tests included blood collection for serology tests (at screening only), hematology and biochemistry
- Vital signs included measurements of blood pressure and pulse, taken at screening and end of study visit

Statistical analyses

- To evaluate bioequivalence of ISAV, an analysis of variance (ANOVA) model with period and formulation as fixed effects and subject as a random effect was fitted on natural logarithmic-transformed AUC_{inf}, AUC_{72}, AUC_{last} and C_{max}
- The test formulation was to be considered bioequivalent to the reference formulation if the 90% confidence intervals (CI) for the geometric least-square (LS) mean ratios of each of the PK parameters were within the range of 80.00% and 125.00%

RESULTS

Patients

- Eighteen subjects (**Table 1**) were randomized in this study of which 10 (55.6%) were male and 8 (44.4%) were female
- The mean age was 37.1 years (range 24 to 52 years). The population was primarily Black or African American [14 (77.8%) subjects]
- Fourteen patients provided plasma concentrations in both periods that were PK evaluable

Pharmacokinetics

- Mean plasma concentration-time profiles of ISAV by formulation are presented in **Figure 1**
- Summary of primary PK parameters of ISAV administered as ISAVUSULF IV solution via NG tube (test formulation) and ISAVUSULF PO capsules (reference formulation) are presented in **Table 2**

Figure 1: Mean (SD) Plasma Concentration of Isavuconazole by Treatment (Linear Scale Plot) (Pharmacokinetic Analysis Set)

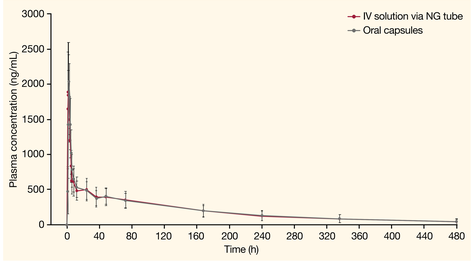

Table 1: Demographic Characteristics of the Study Group

Parameter Category/Statistics	372 mg Isavuconazonium Sulfate Treatment Sequence AB (n = 10)	Treatment Sequence BA (n = 8)	Total (n = 18)
Sex, n (%)			
Male	6 (60.0)	4 (50.0)	10 (55.6)
Female	4 (40.0)	4 (50.0)	8 (44.4)
Ethnicity, n (%)			
Hispanic or Latino	1 (10.0)	0	1 (5.6)
Not Hispanic or Latino	9 (90.0)	8 (100.0)	17 (94.4)
Race, n (%)			
White	2 (20.0)	2 (25.0)	4 (22.2)
Black or African American	8 (80.0)	6 (75.0)	14 (77.8)
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	0	0	0
Age (years)			
Mean (SD)	36.0 (5.9)	38.5 (11.3)	37.1 (8.5)
Median	36.5	38.0	36.5
Min – Max	28 – 43	24 – 52	24 – 52
EudraCT Age Category, n (%)			
≥ 18 years to ≤ 64 years	10 (100)	8 (100)	18 (100)
Weight (kg)			
Mean (SD)	83.47 (15.71)	83.11 (10.01)	83.31 (13.11)
Median	80.75	83.55	82.10
Min – Max	57.6 – 109.2	70.0 – 97.4	57.6 – 109.2
Height (cm)			
Mean (SD)	174.7 (9.4)	169.6 (10.4)	172.4 (9.9)
Median	176.0	171.0	175.0
Min – Max	160 – 188	157 – 182	157 – 188
BMI (kg/m²)			
Mean (SD)	27.11 (2.96)	28.88 (2.09)	27.89 (2.69)
Median	26.35	29.25	28.85
Min – Max	22.5 – 31.3	24.7 – 31.3	22.5 – 31.3

Table 2: Summary of Primary Pharmacokinetic Parameters

Parameter Statistic	Isavuconazonium Sulfate Intravenous Solution via NG Tube (Test Formulation)	Isavuconazonium Sulfate Oral Capsules (Reference Formulation)
AUC_{inf} (h*ng/mL)		
n	14	13
Mean (SD)	99500 (40900)	101000 (44800)
%CV	41.1	44.5
AUC_{72} (h*ng/mL)		
n	14	14
Mean (SD)	36200 (8840)	35800 (8470)
%CV	24.4	23.6
AUC_{last} (h*ng/mL)		
n	14	14
Mean (SD)	88300 (29100)	89000 (30600)
%CV	33.0	34.3
C_{max} (ng/mL)		
n	14	14
Mean (SD)	2320 (529)	2190 (560)
%CV	22.8	25.6

All subjects who were administered at least 1 dose of investigational product for which concentration data were available to facilitate deviation of at least 1 primary pharmacokinetic parameter.
CV: coefficient of variation; SD: standard deviation

Table 3: Statistical Assessment of Bioequivalence of Isavuconazonium Sulfate Intravenous Solution via NG Tube (Test Formulation) Compared to Isavuconazonium Sulfate Oral Capsules (Reference Formulation) (Pharmacokinetic Analysis Set)

Parameter	Isavuconazonium Sulfate Intravenous Solution via NG Tube (Test Formulation) n	Isavuconazonium Sulfate Intravenous Solution via NG Tube (Test Formulation) Geometric LS Mean	Isavuconazonium Sulfate Oral Capsules (Reference Formulation) n	Isavuconazonium Sulfate Oral Capsules (Reference Formulation) Geometric LS Mean	Geometric LS Mean Ratio (%)†	90% CI of Ratio†
AUC_{inf} (h*ng/mL)	14	93300	13	94000	99.31	(92.79, 106.29)
AUC_{72} (h*ng/mL)	14	35200	14	35900	98.09	(92.94, 103.54)
AUC_{last} (h*ng/mL)	14	84500	14	86400	97.72	(92.49, 103.23)
C_{max} (ng/mL)	14	2270	14	2140	106.10	(90.74, 124.00)

†Ratios and confidence limits are transformed back to raw scale and values are expressed as percentages.

- Results of the statistical analysis assessment of the bioequivalence of ISAV between ISAVUSULF IV solution via NG tube (test formulation) compared to ISAVUSULF PO capsules (reference formulation) are presented in **Table 3**
- The geometric LS mean values of C_{max}, AUC_{last}, AUC_{inf}, and AUC_{72} were 106.1%, 97.7%, 99.3% and 98.1%, respectively, of the corresponding PO administration values
- The geometric LS mean ratio and 90% CIs for the C_{max}, AUC_{last}, AUC_{inf}, and AUC_{72} were completely contained within the prespecified limits of 80% to 125%

Safety

- Overall, 11 treatment emergent adverse events (TEAEs) were reported for 3 (17.6%) subjects during the conduct of the study
- One (5.9%) subject experienced TEAEs that led to withdrawal of treatment. The subject experienced single episodes of procedural nausea and procedural vomiting due to the NG tube; both TEAEs were mild in severity. This TEAE occurred concurrently with the NG tube insertion and prior to the subject receiving drug
- There were no TEAEs considered by the investigator to be drug-related
- No potentially clinically significant vital signs measurements were observed or recorded as AEs across sequences
- There were no deaths or SAEs that led to withdrawal of treatment reported during the conduct of this study
- ECG abnormalities (sinus bradycardia, early repolarization normal variant, normal sinus rhythm with sinus arrhythmia, first degree atrioventricular block) were observed across both sequences; however, none of these abnormalities was considered to be clinically significant

CONCLUSIONS

- The geometric LS mean ratios and 90% CI for the AUC_{inf}, AUC_{72}, AUC_{last} and C_{max} of IV solution ISAV administered via NG tube versus PO capsule are completely contained within the prespecified limits of 80% to 125%
- The results demonstrate the bioequivalence of ISAVUSULF IV solution via NG tube (test formulation) and ISAVUSULF PO capsules (reference formulation)
- IV ISAVUSULF solution was used as the test formulation since opening the capsule is highly discouraged because the drug substance is moisture sensitive and hygroscopic and can lead to variable concentrations, depending on the handling of open capsules
- Overall, single doses of 372 mg ISAVUSULF IV solution via NG tube (test formulation) and 372 mg ISAVUSULF PO capsules (reference formulation) under fasting conditions were considered safe and well-tolerable in healthy male and female subjects

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DISCLOSURES

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