CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208901Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA 208901: Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	208901
Priority or Standard	Standard
Submit Date(s)	February 16, 2018
Received Date(s)	February 16, 2018
PDUFA Goal Date	December 16, 2018
Division	Division of Anti-Infective Products
Review Completion Date	November 28, 2018
Established Name	Itraconazole
(Proposed) Trade Name	TOLSURA
Pharmacologic Class	Azole antifungal
Code name	SUBA-itraconazole
Applicant	Mayne Pharma International Pty Ltd.
Formulation(s)	Oral capsule-65 mg
Dosing Regimen	130 mg to 260 mg daily
Applicant Proposed Indication(s)/Population(s)	Treatment of the following fungal infections in immunocompromised and non-immunocompromised patients: 1) Blastomycosis, pulmonary and extrapulmonary 2) Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and 3) Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to Amphotericin B therapy. (b) (4)
Regulatory Action	Approval
Approved Indication(s)/Population(s)	Treatment of the following fungal infections in immunocompromised and non-immunocompromised adult patients: • Blastomycosis, pulmonary and extrapulmonary • Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and • Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy. (b) (4)

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP= Division of Medical Policy

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
BMD	Bone mineral density
BPCA	Best Pharmaceuticals for Children Act
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIP	Division of Anti-infective Products
DMC	data monitoring committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information

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PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event
TEADR	treatment emergent adverse reaction
USPI	US prescribing information
WHO	World Health Organization

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1 Executive Summary

1.1. Product Introduction

Itraconazole is a triazole antifungal drug approved for the treatment of superficial and systemic fungal infections. Similar to other azole antifungals, itraconazole inhibits the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol – a key component of fungal membrane.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In accordance with Section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic Act (the Act), this NDA for TOLSURA 65 mg Capsules was submitted relying on the FDA's findings of safety and effectiveness of the reference listed drug (RLD), Sporanox 100 mg Capsules. The Applicant did not conduct any clinical safety/efficacy trials with TOLSURA Capsules for treatment of systemic fungal infections. The bridge for safety and efficacy from the RLD to TOLSURA Capsules is based on a comparison of the relative bioavailability (BA)/systemic PK exposure between the two itraconazole drug products.

The Applicant conducted 4 relative BA/PK studies to compare the steady-state exposure of itraconazole following administration of TOLSURA vs. SPORANOX Capsules under fed conditions for both products. The doses of TOLSURA used in these BA/PK studies ranged from 130 mg to 390 mg per day, which were designed to provide similar PK exposure as the approved dosing regimens of the RLD for the systemic fungal indications (200 mg to 400 mg per day). Overall, the steady-state AUC and Cmax of itraconazole following administration of TOLSURA were comparable to Sporanox under fed conditions. Thus, the Clinical Pharmacology review team concluded that an acceptable PK bridge has been demonstrated between TOLSURA Capsules and Sporanox Capsules.

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1.3. Benefit-Risk Assessment

Benefit-Risk and Summary Assessment

The Applicant submitted this 505(b)(2) NDA for TOLSURA 65 mg capsules (also known as SUBA-itraconazole), a new capsule formulation of itraconazole. Itraconazole (TOLSURA™ 65 mg Capsules) is an azole antifungal drug. The proposed indications are for the treatment of the following approved indications of the RLD, Sporanox 100 mg Capsules: fungal infections in immunocompromised and non-immunocompromised patients: blastomycosis, pulmonary and extrapulmonary histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy in adults.

The Applicant submitted relative BA/PK studies in healthy subjects which demonstrated comparative steady-state BA/PK exposure between TOLSURA 65 mg Capsules and Sporanox 100 mg Capsules across the full dosing range of the RLD, specifically: 2 TOLSURA capsules three times a day for three days (Study MPG013); 2 TOLSURA capsules once a day (Study MPG012); 2 TOLSURA capsules twice a day (Study MPG015). The Applicant also conducted a steady-state food effect study (Study MPG017) and a drug-drug interaction study to investigate the impact of co-administration of omeprazole on the bioavailability of TOLSURA Capsules (Study MPG016). Overall, the results of the BA/PK studies showed that TOLSURA had comparable steady-state C_{max} and AUC as compared with Sporanox capsules when both products were given under fed conditions.

The safety profile of itraconazole is well-established in adult patients and reflected in the current approved product labeling for the RLD. The safety data in healthy subjects submitted in this NDA demonstrate that the TOLSURA safety profile was comparable to that of the RLD, although the safety database was small. This 505(b)(2) NDA relies on FDA previous findings of itraconazole safety for the approved indications listed above based on the comparable exposure between TOLSURA and the RLD.

Notable serious adverse reactions with itraconazole include: congestive heart failure (Boxed Warning), potential life-threatening drug interactions with drugs metabolized by certain CYP450 enzymes (Boxed Warning), hepatotoxicity, peripheral neuropathy, and hearing loss. Common adverse reactions noted in the RLD labeling (incidence ≥ 1%) are nausea, rash, vomiting, edema, headache, diarrhea, fatigue, fever, pruritus, hypertension, abnormal hepatic function, abdominal pain, dizziness, hypokalemia, anorexia, malaise, decreased libido, somnolence, albuminuria, impotence. In the studies reviewed for this NDA, the healthy subjects tolerated TOLSURA and the RLD well. The incidence rate (≤ 1%) of dropouts or discontinuations related to adverse reactions was low. The adverse reactions were mild

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to moderate in severity. No deaths or serious adverse reactions were reported.
In conclusion, approval of TOLSURA 65 mg capsules under Section 505(b)(2) for the treatment of blastomycosis, pulmonary and extrapulmonary histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy in adults is supported by the results of the comparative bioavailability and pharmacokinetic studies between TOLSURA 65 mg Capsules and the RLD, Sporanox 100 mg capsules and the Agency's previous findings of safety and effectiveness of Sporanox and the published literature.

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Table 1 Benefit Risk Assessment for TOLSURA

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Systemic endemic mycoses (blastomycosis, and histoplasmosis) are common in specific geographical areas of the world. Blastomycosis is an infection caused by a fungus called *Blastomyces*. CDC reports that most cases occur in the United States and Canada. Yearly incidence rates are approximately 1 to 2 cases per 100,000 population. • Histoplasmosis is an infection caused by a fungus called *Histoplasma*. The fungus lives in the environment, particularly in soil that contains large amounts of bird or bat droppings. In the United States, *Histoplasma* mainly lives in the central and eastern states, especially areas around the Ohio and Mississippi River valleys. The fungus also lives in parts of Central and South America, Africa, Asia, and Australia. Many people who get histoplasmosis will get better on their own without medication, but in some patients who are immunocompromised, the infection can become severe. CDC reports the incidence of histoplasmosis in adults aged 65 years and older in the U.S. to be 3.4 cases per 100,000 population. Rates were highest in the Midwest, with an estimated 6.1 cases per 100,000 population. • Invasive aspergillosis is uncommon and occurs primarily in immunocompromised people. The first population-based incidence estimates for invasive aspergillosis obtained from laboratory surveillance suggested a yearly rate of 1 to 2 cases of aspergillosis per 100,000 population. However, the epidemiology	• If left untreated, particularly in immunocompromised patients, systemic fungal infection can spread to the skin, lungs, and nervous system, leading to significant complications, such as widespread skin lesions, asthma, allergic bronchopulmonary diseases, and meningitis. • Early diagnosis and prompt treatment can alleviate the systemic fungal infections symptoms and signs, and prevent serious complications.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of invasive *Aspergillus* infections has likely shifted since this time due to the increasing number of solid organ and stem cell transplant recipients and newer immunosuppressive agents.	
Current Treatment Options	• Other azole antifungals including fluconazole, voriconazole or posaconazole share approved indications for the treatment of systemic endemic mycoses infections.	• TOLSURA can be an alternative to Sporanox 100 mg capsules in situations such as shortage.
Benefit	• TOLSURA 65 mg capsules under fed conditions has a pharmacokinetic profile comparable to that of the RLD.	• TOLSURA is likely to provide benefit similar to the RLD for the indications being sought based on the comparable systemic exposure profile.
Risk	• The safety profile of itraconazole is described in the RLD, Sporanox 100 mg capsules, product labeling. • The safety data for TOLSURA in healthy subjects submitted in this NDA demonstrate a safety profile comparable to that of the RLD. • Serious adverse reactions in the Boxed Warning section of the TOLSURA label include congestive heart failure and drug interactions.	• Prescribing information for TOLSURA includes the information in the Sporanox labeling. • Limitations of use in the Indications and Usage Section: ○ TOLSURA is not indicated for the treatment of onychomycosis ○ TOLSURA is **NOT** interchangeable or substitutable with other itraconazole products
Risk Management	• Serious adverse reactions associated with use of itraconazole are described in the product labeling along with recommendations for monitoring and mitigation strategies.	• Safety information is adequately communicated in labeling. No additional risk management strategies are needed.

1.4 Patient Experience Data

Not applicable. There is no patient experience data submitted to this application.

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2 Therapeutic Context

2.1. Analysis of Condition

Histoplasmosis is a common endemic mycosis that is usually asymptomatic but occasionally results in severe illness. Histoplasmosis and its causative agent, *Histoplasma capsulatum*, are found worldwide but particularly in North and Central America. Within the United States, infection is most common in the Midwestern states located in the Ohio and Mississippi River valleys. Incidence is highest in the Midwest, with an estimated 6.1 cases per 100,000. Among the endemic mycoses, it is the most common cause for hospitalization.

Blastomycosis is a systemic pyogranulomatous infection, primarily involving the lungs, that arises after inhalation of the conidia of *Blastomyces dermatitidis* or *Blastomyces gilchristii*. Most cases of blastomycosis have been reported in North America. Yearly incidence rates are approximately 1 to 2 cases per 100,000. Blastomycosis of the lung can be an asymptomatic infection or can manifest as acute or chronic pneumonia. Hematogenous dissemination frequently occurs; extrapulmonary disease of the skin, bones, and genitourinary system is common, but almost any organ can be infected.

Invasive aspergillosis occurs primarily in immunocompromised hosts. Neutropenia and glucocorticoid use are the most common predisposing factors. The infecting species is most commonly *Aspergillus fumigatus*, but other species, including *A. flavus*, *A. terreus*, and *A. niger*, also cause disease.

2.2. Analysis of Current Treatment Options

There are other FDA approved antifungal drugs used for the treatment of aspergillosis, histoplasmosis, and blastomycosis as listed in Table 2. Liposomal Amphotericin B and deoxycholate Amphotericin B formulation are used off-label for treatment of blastomycosis and histoplasmosis.

Table 2: Summary of Treatment Armamentarium Relevant to Proposed Indications

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments					
Aspergillosis					
Voriconazole	Invasive aspergillosis	2002	Loading dose: IV 6 mg/kg q12h for the first 24 hours Maintenance Dose: IV- 4 mg/kg q12h Oral- 200 mg q12h	Common adverse reactions (incidence ≥2%): visual disturbances, fever, nausea, rash, vomiting, Chills, liver function test abnormal, tachycardia,	Use only in patients 12 years of age and older.

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Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
				hallucinations	
Isavuconazonium	Invasive aspergillosis	2015	Loading Dose: 372 mg isavuconazonium sulfate q 8 hours for 6 doses oral or IV. Maintenance Dose: 372 mg isavuconazonium sulfate once daily oral or IV, 12 to 24 hours after the last loading dose.	Most frequent ARs: nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain	Use only in 18 years of age and older.
Amphotericin B (deoxycholate)	Aspergillosis	1971	0.6 mg/kg/d	Nephrotoxicity; hepatotoxicity; infusion related reactions	Use in adult and pediatric patients
Liposomal Amphotericin	Treatment of patients with Aspergillus species, refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate.	1997	3-5 mg/kg IV	Nephrotoxicity; Amphotericin B-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine) due to hypokalemia; GI symptoms (diarrhea, nausea, vomiting and abdominal pain); fever; and rash	Use in adults and pediatric patients
Caspofungin	Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies	2001	Single 70-mg IV loading dose on Day 1, followed by 50 mg once daily thereafter.	The following ARs were observed with an incidence of 12.5% or greater: blood alkaline phosphatase increased, hypotension, respiratory failure, pyrexia, diarrhea, nausea, headache, ALT increased, AST increased, blood bilirubin increased, and blood potassium decreased; pulmonary edema, ARDS, and radiographic infiltrates.	Use in adults and pediatric patients (3 months of age and older)
Histoplasmosis (Reviewer's Comment: Amphotericin B liposomal and deoxycholate formulation Ampho B are used off-label for histoplasmosis and blastomycosis. IDSA Clinical Practice Guidelines recommend them as preferred treatment for moderate to severe acute pulmonary histoplasmosis and blastomycosis. Fluconazole, voriconazole, and posaconazole are used off-label as second-line treatment for blastomycosis and histoplasmosis.)[2]					
Lipid formulation of	Moderate to severe acute	1997	3.0–5.0 mg/kg daily intravenously for	Nephrotoxicity and GI symptoms	Use in adult and pediatric patients.

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Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
amphotericin B	pulmonary histoplasmosis		1–2 weeks followed by itraconazole 200 mg 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks is recommended		
Deoxycholate formulation of amphotericin B	Moderate to severe acute pulmonary histoplasmosis	1971	0.7–1.0 mg/kg daily IV) is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity.	Nephrotoxicity; GI symptoms.	Use in adult and pediatric patients.
Ketoconazole	Mild manifestations of histoplasmosis but not in cases of disseminated or CNS disease.	1981	Single daily administration of 200 mg (one tablet). If clinical responsiveness is insufficient within the expected time, the dose may be increased to 400 mg (two tablets) once daily. Children: single daily dose of 3.3 to 6.6 mg/kg	Serious hepatotoxicity; and QT prolongation	Use in adult and children over 2 years of age.
Blastomycosis					
Amphotericin B	Moderate to severe disease, central nervous system disease, immunosuppressed patients	1997	Lipid formulation of amphotericin B (AmB) at a dosage of 3–5 mg/kg per day or AmB deoxycholate at dosage of 0.7–1 mg/kg per day for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of 6–12 months, is recommended	Nephrotoxicity and GI symptoms	IDSA guidelines states that Ampho B can be used in pregnant women and neonates with blastomycosis.

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Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues	Other Comments
Ketoconazole	Blastomycosis (mild)	1981	Single daily administration of 200 mg (one tablet). If clinical responsiveness is insufficient within the expected time, the dose may be increased to 400 mg (two tablets) once daily. Children: single daily dose of 3.3 to 6.6 mg/kg	Serious hepatotoxicity; and QT prolongation	Use in adult and children over 2 years of age.
Off-Label Treatments (Second line treatment for Histoplasmosis and Blastomycosis)[2,3]					
Fluconazole	Histoplasmosis and blastomycosis	1990	800 mg daily for 12 weeks as induction therapy, followed by 400 mg daily.	Treatment-related clinical adverse events occurred at an incidence of (≥1%) nausea, headache, skin rash, vomiting, abdominal pain, and diarrhea.	Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.
Voriconazole	Blastomycosis and Histoplasmosis	2002	200–400 mg twice a day for at least 12 months	Common ARs (incidence ≥2%): visual disturbances, fever, nausea, rash, vomiting, chills, liver function test abnormal, tachycardia, and hallucinations	Use only in patients 12 years of age and older.
Posaconazole	Histoplasmosis and Blastomycosis	2006	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.	Common treatment-emergent adverse reactions in studies with posaconazole are diarrhea, nausea, fever, vomiting, headache, coughing, and hypokalemia	Posaconazole should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

[1] Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. AnnIntern Med 2002; 137:105–9.

[2] Joseph Wheat ,Alison G. Freifeld, Martin B. Kleiman, John W. Baddley, David S. McKinsey,James E. Loyd,and Carol A. Kauffman: Clinical Practice Guidelines for the Management of Patients with Histoplasmosis: 2007 Update by the Infectious Diseases Society of AmericaClinical Infectious Diseases 2007; 45:807–25.

[3] Stanley W. Chapman, William E. Dismukes, Laurie A. Proia, Robert W. Bradsher, Peter G. Pappas, Michael G. Threlkeld, Carol A. Kauffman; Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America, *Clinical Infectious Diseases*, Volume 46, Issue 12, 15 June 2008, Pages 1801–1812,

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3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Reference listed drug (RLD), Sporanox® (itraconazole) Capsules, 100 mg, is currently marketed in the U.S. and worldwide. The proposed drug product is not currently marketed in the U.S. or elsewhere.

This application is a resubmission after a Refuse-to-File action because the application lacked the data to adequately bridge the proposed product to the relied-upon listed drug (RLD), Sporanox®. No clinical efficacy or safety studies were submitted in the NDA for the proposed systemic fungal indications.

The proposed drug product is not being developed for an onychomycosis indication.

3.2 Summary of Presubmission/Submission Regulatory Activity

October 23, 2007: Pre-IND meeting held with the Division of Anti-Infective Products (DAIP) and the Division of Dermatology and Dental Products (DDDP).

(b) (4)

February 11, 2011: The Sponsor's name changed to Mayne Pharma Group Limited.

August 22, 2011: An EOP2 meeting was held under INDs 78675 and 101498. The Sponsor provided data from five US studies: 10850702, 10850703, 10850705, 10850706, and 70850702 and two European studies: HGN007 and HGN008. Study 70850702 evaluated safety and efficacy while the other studies were PK studies. FDA did not agree that the clinical pharmacology studies were adequate. The Sponsor did not provide data to adequately bridge the proposed product to Sporanox®.

(b) (4)

November 6, 2012: A Pre-NDA meeting was held under IND 78675 to reach agreement on a clinical development plan that would support the filing of a 505(b)(2) NDA (b) (4) . Of note, the Sponsor proposed developing a 65 mg capsule

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(b) (4). FDA required that Study 10850703 be repeated using the 65 mg capsule. FDA concluded that a Phase 3 trial would not be required if studies with the 65 mg capsule provide sufficient scientific evidence to rely on the innovator product. The Sponsor will not propose the onychomycosis Study 70850702 to be a pivotal trial. FDA acknowledged that itraconazole is a highly variable drug and bioinequivalence is a possibility.

February 18, 2013: The Sponsor requested a Special Protocol Assessment of proposed clinical Study MPG009, "The Relative Bioavailability of Single Oral doses of SUBA™-itraconazole 65 mg Capsules (Mayne) compared to SPORANOX® (itraconazole) 100 mg Capsules (Janssen) administered under Fasted and Fed conditions in Healthy Adult Volunteers."

April 5, 2013: FDA agreed that the design and planned analysis of Study MPG009 would adequately address the objectives necessary to support a regulatory submission and issued a Special Protocol – Agreement.

December 5, 2013: A Guidance meeting was held under IND 78675. Of note, FDA strongly recommended that the Sponsor conduct the multiple dose PK Study MPG010 to assess the steady-state systemic PK and variability of SUBA™-itraconazole 65 mg Capsules when dosed at the proposed clinical dosage regimen relative to the approved dosage regimen of Sporanox® Capsules under both fed and fasted conditions.

February 19, 2014: A Guidance meeting was held to discuss FDA's review of the Sponsor's Population PK model. FDA agreed that the population PK analysis did provide additional information, but recommended that utilizing the PK, safety, and tolerability data obtained from Study MPG010 along with population PK modeling would be more informative.

November 30, 2015: The Sponsor submitted NDA 208901 for itraconazole capsules, (b) (4) 65 mg.

December 11, 2015: Sponsor submitted a new Phase 1 study Protocol, Study MPG012, "An open label, randomized, two-treatment, two-sequence, two-period, cross-over, multiple-dose, steady -state, oral bioavailability study of SUBA™ (itraconazole capsules 2x65 mg; test) and Sporanox® (itraconazole capsules 2x100 mg; reference) in healthy, adult, human subjects under fed conditions." FDA concluded that the protocol was acceptable but was only a partial of the Study MPG010 that had been recommended in previous meetings with the Sponsor.

January 29, 2016: FDA issued a Refuse-to-File action for NDA 208901 under 21 CFR 314.101(d) for the reasons stated above under Section 1.1, U.S. Regulatory Actions and Marketing History.

April 4, 2016: A meeting was held to discuss issues raised in the Refuse-to-File letter. FDA recommended the Sponsor submit protocols for Studies MPG010, MPG011, and MPG012 for review and when completed, submit the data from the three studies at the same time.

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December 14, 2016: A Pre-NDA meeting was held under IND 78675 to discuss whether the new studies conducted since the April 4, 2016, meeting adequately addressed the RTF issues listed in the January 26, 2016 RTF letter. Food effect studies, gastric acid reducers/neutralizers, blood sampling time points, US versus Australian-sourced RLD, and potential labeling issues were discussed. The Division agreed that based on the completed and proposed studies presented in the briefing package, the exposure bridge was likely to be covered for the proposed drug product.

December 18, 2017: A Pre-NDA meeting was held. FDA agreed that NDA 208901 could be resubmitted.

February 16, 2018: The Sponsor resubmitted NDA 208901.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

No clinical site inspections were required for this NDA.

4.2 Product Quality

Novel excipients: No

Any impurity of concern: No

Sufficient controls to insure safety and efficacy of the commercial product: Yes

The drug product, TOLSURA (itraconazole capsules) 65 mg, is an immediate release (b) (4) filled oral capsule. (b) (4)

All excipients are compendial grade and comply with the requirements of the USP/NF monographs except for the gelatin capsule shell. The gelatin capsule shells are made from (b) (4)

The formulation, image and manufacturing site for the clinical and stability batches are the same as those proposed for commercial manufacture.

The shelf-life and storage conditions for itraconazole capsules 65 mg are listed below.

- For itraconazole capsules 65 mg stored in the proposed HDPE bottles, the proposed shelf-life of 36 months is acceptable if stored at controlled room temperature 15°-25°C (59°-77°F) and protected from light and moisture.
- (b) (4)

This NDA is recommended for **Approval** from the Product Quality perspective. All Product Quality aspects including facilities are found acceptable.

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Table 3

Drug Product Composition

Component	Grade	Quantity (mg/capsule)	Function
Itraconazole	USP/Ph.Eur.	(b) (4)	
Hypromellose Phthalate (b) (4)	NF/Ph.Eur.		
Sodium Starch Glycolate (b) (4)	NF/Ph.Eur.		
Colloidal Silicon Dioxide (b) (4) (b) (4)	NF/Ph.Eur.		
Magnesium Stearate (b) (4)	NF/Ph.Eur.		
(b) (4)	NF/Ph.Eur.		
	NF		
Capsule size No 1 (b) (4) Light Blue Cap/White Body	In-house		
(b) (4)	21 CFR		
	21 CFR		
Gelatin	USP/Ph.Eur.		
(b) (4)	Proprietary		
	NF		
	USP		
	USP		
	NF		
	USP		
	NF		
	NF		
	NF		
	USP		
		(b) (4)	

4.3 Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

No new pharmacology/toxicology or nonclinical pharmacokinetic studies were conducted for this NDA. The information referenced below is from the SPORANOX® (itraconazole) capsules labeling and published literature.

Pharmacology

Primary pharmacodynamics

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Itraconazole inhibits the cytochrome P450-dependent, ^{14}C-demethylation step in the synthesis of ergosterol, a vital component of fungal cell membranes. This inhibition is believed to result in accumulation of 14-alpha-methylsterols.

Secondary pharmacodynamics
Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. Co-administration of a number of CYP3A4 substrates are contraindicated with SPORANOX®.

Safety Pharmacology
When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. This finding is consistent with the results from a healthy volunteer study of itraconazole intravenous infusion, in which transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging. It is not clear if these findings after intravenous itraconazole indicate a risk to patients taking oral itraconazole formulations.

Pharmacokinetics

Absorption
Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 3 to 6 hours following a single oral dose in rats, rabbits and dogs.

Distribution
Most of the itraconazole in plasma (>99%) is bound to protein (mainly albumin). It has also a marked affinity for lipids. Itraconazole is distributed in a large apparent volume in the body (>700 L), suggesting extensive distribution into tissues.

Concentrations in lung, kidney, liver, bone, stomach, spleen, muscle and skin were higher than corresponding concentrations in plasma. Concentrations in the cerebrospinal fluid were much lower than in plasma.

Metabolism
Itraconazole is extensively metabolized by the liver into several metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole and that the main metabolite is hydroxy-itraconazole.

Excretion
Itraconazole is excreted largely as metabolites via the feces, with a smaller percentage excreted via urine. Unchanged drug constitutes a small portion of the fecal excretion and an even smaller portion of its urinary excretion.

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Toxicology
Adverse events of special interest include adrenal gland changes, bone defects, carcinogenicity and teratogenicity.

In a 3-month study in rats, adrenal gland and ovarian hypertrophy were observed, with histopathology evaluations revealing foamy cells containing proteinaceous materials. This finding is consistent with phospholipidosis, a common effect in cationic amphiphilic drugs (CADs), including several azole antifungal drugs such as ketoconazole and posaconazole. Steroid-producing cells of the adrenal cortex, testis and ovaries are in particular susceptible to drug-induced phospholipidosis. A 3-month study in dogs showed changes in the adrenals and thymus.

In three toxicology studies using rats, itraconazole induced bone defects (reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility) at 20 mg/kg/day. Higher doses (80 mg/kg over 1 year or 160 mg/kg/day for 6 months) induced small tooth pulp with hypocellular appearance in some rats. The long-term effects of itraconazole on bone growth in children are unknown.

Carcinogenicity
In a rat carcinogenicity study, male rats treated with 25 mg/kg/day had a slightly increased incidence of soft tissue sarcoma. These sarcomas may represent a species-specific consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. The increase in incidence was not statistically significant but the finding is considered significant since squamous cell carcinoma in the lung is extremely uncommon in untreated rats. Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day.

Reproductive and developmental toxicity
Itraconazole crosses the placenta in rat. Dose-related increases in maternal toxicity, embryotoxicity, and teratogenicity were observed in rats at 40-160 mg/kg/day, and in mice at 80 mg/kg/day. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

Genetic Toxicology
Itraconazole produced no mutagenic effects when assayed in DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo

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fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Recommendation

There are no nonclinical data that preclude the approval of TOLSURA.

5.2 Referenced NDAs, BLAs, DMFs

NDA 20083 (Sporanox [itraconazole] capsules)

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6 Clinical Pharmacology

6.1 Executive Summary

SUBA™ is a proprietary formulation technology designed to enhance solubility and absorption of highly insoluble drugs. Itraconazole is a drug with low aqueous solubility and poor bioavailability. Mayne Pharma has applied its SUBA™ technology to develop a supra-bioavailable formulation of itraconazole (SUBA™ Itraconazole Capsules), with the proposed tradename TOLSURA Capsules. TOLSURA 65 mg Capsules were designed to have (i) better-controlled bioavailability, (ii) lower inter- and intra-patient variability, and (iii) a more reliable product in both high absorbing and low absorbing individuals to the benefit of the patients. The '*relied upon listed drug*' (RLD) is SPORANOX Capsules 100 mg, marketed by Janssen and was approved in the USA in 1992 (NDA 020083). The proposed total daily doses of TOLSURA range between 130 to 390 mg depending on the specific indication. For comparison, SPORANOX capsule doses for the same indications range between 200 to 600 mg.

Although the active substance, pharmaceutical form and route of administration are the same, TOLSURA 65 mg Capsules cannot be considered a "generic medicinal product" as they do not have the same "quantitative or qualitative composition in terms of active substance" as the RLD. In accordance with Section 505(b)(2) of the of the Federal Food, Drug, and Cosmetic Act (the Act), and with 21 CFR 314.54, this new drug application for TOLSURA 65 mg Capsules was submitted relying on the FDA's finding of safety and effectiveness of the RLD. Thus, the Applicant did not conduct any clinical safety / efficacy trials with TOLSURA Capsules for treatment of systemic fungal infections. The bridge for safety and efficacy from the RLD to TOLSURA Capsules is based solely on a comparison of the relative bioavailability/systemic PK exposure between the two itraconazole drug products.

In light of this, the Applicant conducted 4 relative bioavailability (BA) studies to compare the exposure of itraconazole following administration of TOLSURA vs. SPORANOX Capsules. In addition to the 4 BA studies the applicant also conducted a fed vs. fasted study and a DDI trial to evaluate the effect of co-administration of omeprazole on the BA of TOLSURA Capsules. Additionally, a population PK analysis was conducted by the Applicant. A tabular description of the studies conducted by the Applicant is given below:

Table 4 Clinical Studies Conducted

Study Number	N	Dose (TOLSURA)	Dose (SPORANOX)	Fed/Fasted	Dosing frequency
MPG009	52	1 x 65 mg	1 x 100 mg	Fed and Fasted	Single dose
MPG012	24	2 x 65 mg	2 x 100mg	Fed	Once daily for 14 days

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Study Number	N	Dose (TOLSURA)	Dose (SPORANOX)	Fed/Fasted	Dosing frequency
MPG013	16	2 x 65 mg	2 x 100mg	Fed	Three times daily for 3 days and once on Day 4
MPG015	24	2 x 65 mg	2 x 100mg	Fed	Twice daily for 14 days
MPG016	30	2 x 65 mg	-	Fasted	Single dose of TOLSURA given alone and with omeprazole administered once daily for 7 days
MPG017	24	2 x 65 mg	-	Fed and Fasted	One daily for 14 days

The Office of Study Integrity and Surveillance (OSIS) recommended acceptance of data from the bioanalytical sites without an on-site inspection. Please refer to OSIS's review dated June 01, 2018 for details.

Results from the relative BA studies indicated that the mean steady-state systemic exposure to itraconazole was 10 to 22% higher following administration of TOLSURA as compared to that of SPORANOX when both products were given under fed conditions. The results of Study MPG-012 indicated that following once-daily repeat dose administration of 130 mg of TOLSURA (2 x 65 mg QD) under fed conditions, the mean steady-state C_{max} and AUC of itraconazole was about 22% and 15% higher, respectively, than that following repeat dose administration of 200 mg QD of the RLD (2 x 100 mg SPORANOX). Results from Study MPG015 indicated that when TOLSURA was administered under fed conditions at a dose of 130 mg BID (2 x 65 mg BID), the mean steady-state C_{max} and AUC of itraconazole were 12% and 11% higher, respectively, than that observed following administration of 200 mg BID of the RLD (2 x 100 mg BID SPORANOX). Results from Study MPG-013 indicated that when TOSURA was administered under fed conditions at a dose regimen of 390 mg/day (2 x 65 mg TID) x 3 days, followed by 130 mg on Day 4, the mean steady-state C_{max} and AUC of itraconazole was 15% and 10% higher, respectively, than that observed following administration of the RLD given at a dose regimen of 600 mg/day (3 x 200 mg TID) x 3 days, followed by 200 mg on Day 4.

Based on a review of the studies conducted by the Applicant, it was observed that the systemic exposure of itraconazole following administration of SPORANOX was 20-40% lower than that reported in the approved US labeling for SPORANOX capsules following a unit dose of either 100 mg or 200 mg. The reasons for this are not known. Furthermore, the RLD is recommended to be taken with food to increase bioavailability of itraconazole. However, in the studies

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conducted by the Applicant (e.g., Study MPG-009), it was observed that the C_{max} and AUC of itraconazole following administration of both TOLSURA and SPORANOX Capsules with food were lower, as compared to fasted conditions. The reasons for this decrease in systemic exposure of itraconazole with food in the studies conducted by the Applicant are also unknown.

Upon request by the FDA Review Division (DAIP), the relative BA studies to compare the steady-state systemic exposure of itraconazole following administration of TOLSURA versus the RLD were conducted under fed conditions. Given that the systemic exposure of itraconazole was demonstrated to be comparable between TOLSURA and SPORANOX Capsules under fed conditions, whereas exposure was significantly higher for TOLSURA under fasted conditions, TOLSURA Capsules will be recommended to be taken only under fed conditions.

The pharmacometric review focused on assessing the population PK analysis of itraconazole for TOLSURA and SPORANOX that included single and multiple doses of TOLSURA in healthy adult subjects. The population PK (Pop PK) analysis conducted by the Applicant and verified by the Clinical Pharmacology review team, indicated that TOLSURA has less variability in exposure (AUC and C_{max}) than SPORANOX, which equates to an approximate 30-35% reduction in exposure variability for TOLSURA compared to SPORANOX. Thus, the Clinical Pharmacology review team is in agreement with these Pop PK results and the Applicant's conclusions regarding the PK variability of TOLSURA vs. SPORANOX.

An exposure-response analysis between itraconazole exposure and adverse events associated with TOLSURA was also explored by the Clinical Pharmacology review team. There was no clear exposure-response relationship for adverse events with TOLSURA at the doses evaluated (i.e., 130 mg to 390 mg) and duration of dosing (i.e., 3 to 15 days) that were evaluated in the healthy subject PK/BA studies.

Overall, the systemic exposure of itraconazole, in terms of steady-state AUC, following administration of TOLSURA was slightly higher than the RLD (i.e., approximately 10% to 15% higher). The steady-state C_{max} of itraconazole was 12% to 22% higher following administration of TOLSURA compared to the RLD. However, it is noteworthy that the highest steady-state C_{max} of itraconazole (1.7 mcg/mL) following administration of TOLSURA seen in the BA/PK studies conducted by the Applicant was observed to be slightly lower than the highest C_{max} reported in the FDA approved labeling for SPORANOX (2 mcg/mL) when dosed at 200 mg BID. Thus, the increase in C_{max} with TOLSURA seen in the relative BA/PK studies conducted by the Applicant is deemed to be acceptable from a Clinical Pharmacology perspective, in terms of safety. In light of these results, the Clinical Pharmacology review team concludes that an acceptable PK bridge has been demonstrated between TOLSURA Capsules and the RLD, SPORANOX Capsules.

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6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

Treatment of Blastomycosis and Histoplasmosis: The recommended dose is 130 mg once daily (2 x 65 mg capsules) with food. If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65 mg increments to a maximum of 260 mg daily. Doses above 130 mg/day should be given in two divided doses.

Treatment of Aspergillosis: A daily dose of 130 (2 x 65 mg) to 260 mg (4 x 65 mg) is recommended to be administered with food. Doses above 130 mg/day should be given in two divided doses.

Treatment in Life-Threatening Situations: In life-threatening situations, a loading dose should be used, i.e., loading dose of 130 mg (2 x 65 mg capsules) three times daily (390 mg/day) is given for the first 3 days of treatment. Starting on Day 4 of treatment, TOLSURA doses above 130 mg/day should be given in two divided doses. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

6.3.2 Clinical Pharmacology Questions

What is the proposed to-be-marketed formulation, proposed indications, and dosing regimens of TOLSURA Capsules?
As per the Applicant's description in the NDA, SUBA™ is a proprietary formulation technology designed to enhance the solubility and hence the oral bioavailability of highly insoluble drugs, such as itraconazole. The underlying principle of the technology is to produce a solid dispersion of a poorly soluble drug in a polymer. SUBA™ technology has been applied to improving the

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oral absorption of itraconazole [redacted] (b) (4)

The proposed to-be-marketed formulation of TOLSURA Capsules is a 65 mg [redacted] (b) (4) filled capsule [redacted] (b) (4) Although no clinical efficacy/safety trials were conducted with TOLSURA capsules, the proposed systemic fungal indications for TOLSURA capsules are the same as that for SPORANOX Capsules. The dosing regimens for TOLSURA Capsules are as follows:

Treatment of Blastomycosis and Histoplasmosis
The recommended dose is 130 mg once daily (2 x 65 mg capsules) with food. If there is no obvious improvement, or there is evidence of progressive fungal disease, the dose should be increased in 65 mg increments to a maximum of 260 mg daily. Doses above 130 mg/day should be given in two divided doses.

Treatment of Aspergillosis
A daily dose of 130 (2 x 65 mg) to 260 mg (4 x 65 mg) is recommended to be administered with food. Doses above 130 mg/day should be given in two divided doses.

Treatment in Life-Threatening Situations
In life-threatening situations, a loading dose should be used, i.e., loading dose of 130 mg (2 x 65 mg capsules) three times daily (390 mg/day) is given for the first 3 days of treatment. Starting on Day 4 of treatment, TOLSURA doses above 130 mg/day should be given in two divided doses. Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

What is the relative bioavailability of itraconazole following the administration of TOLSURA versus SPORANOX capsules under fed conditions at steady-state?
The applicant has assessed the steady-state bioavailability of TOLSURA capsules relative to SPORANOX (100 mg capsules) under fed conditions.

The results for Study MPG012 in Table 5 below indicate that following QD administration of 130 mg of TOLSURA Capsules, the steady state C_{max} and AUC of itraconazole is 22% and 15% higher, respectively, when compared to 200 mg QD of SPORANOX Capsules (2 X 100 mg). This difference is deemed by the Clinical Pharmacology review team as clinically insignificant.

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Table 5. MPG012: TOLSURA Capsules 130 mg [2 X 65mg] vs. SPORANOX Capsules 100 mg [2 X 100mg] dosed QD for 15 days in 20 healthy volunteers under fed conditions

Parameter	Test	RLD	Ratio Test/RLD	90% C.I.
$C_{max\ ss}$ (ng/mL)	566.2 ± 215.1	463.2 ± 176.0	122.2%	99.9, 149.6
C_{trough} (ng/mL)	213.2 ± 47.97	214.5 ± 48.3	99.4%	87.9, 112.4
AUC_{tau} (ng-h/mL)	7723.2 ± 2818.9	6717.5 ± 2451.9	115.0%	94.6, 139.7

Source: Adapted from Applicant's Biopharm Summary

As seen in Table 6 for Study MPG013, the $C_{max\ ss}$ and AUC_{tau} of itraconazole following oral doses of 390 mg/day x 3 days, then 130 mg on Day 4 of TOLSURA are comparable to that of SPORANOX following oral doses of 600 mg/day x 3 days, followed by 200 mg on Day 4, in healthy, adult, human subjects under fed conditions. The small increases in C_{max} (15%) and AUC (10%) with TOLSURA are deemed by the Clinical Pharmacology review team as clinically insignificant.

Table 6. MPG013: TOLSURA Capsules 130 mg [2 X 65mg] vs. SPORANOX Capsules 100 mg [2 X 100mg] dosed TID from Days 1-3 and QD on Day 4 in 15 healthy volunteers under fed conditions

Parameter	Test	RLD	Ratio Test/RLD	90% C.I.
$C_{max\ ss}$ (ng/mL)	1055.3 ±276.9	921.3 ± 254.4	114.6%	103.4, 126.9
C_{trough} (ng/mL)	881.1 ± 296.0	820.6 ± 255.4	107.3%	95.6, 120.6
AUC_{tau} (ng-h/mL)	6881.7 ± 2144.4	6236.2 ± 1688.4	110.3%	100.1, 121.7

Source: Adapted from Applicant's Biopharm Summary

The results in Table 7 for Study MPG015 indicate that the steady-state C_{max} and AUC_{tau} of itraconazole following oral doses of 130 mg (2 X 65mg) BID TOLSURA are comparable to that of SPORANOX following oral doses of 200 mg dosed BID, in healthy, adult subjects under fed conditions. The small increases in C_{max} (12%) and AUC (11%) with TOLSURA are deemed by the Clinical Pharmacology review team as clinically insignificant.

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Table 7. MPG015: TOLSURA Capsules 130 mg [2 X 65mg] vs. SPORANOX capsules 200 mg [2 X 100mg] dosed BID in for 14 days followed by once on Day 15 in 16 healthy volunteers under fed conditions

Parameter	Test	RLD	Ratio Test/RLD	90% C.I.
$C_{max\ ss}$ (ng/mL)	1632.2 ± 370.8	1457.5 ± 400.1	112.0%	104.9, 119.6
C_{trough} (ng/mL)	1187.4 ± 356.7	1004.9 ± 254.7	118.1%	110.2, 126.7
AUC_{tau} (ng-h/mL)	15562.1 ± 3681.1	14065.1± 3772.8	110.6%	104.0, 117.7

Source: Adapted from Applicant's Biopharm Summary

Overall, the AUC of itraconazole following repeat administration of TOLSURA with food was comparable to the RLD. The C_{max} of itraconazole following administration of 130 mg BID of TOLSURA with food was about 22% higher than the C_{max} following 200 mg BID administration of SPORANOX capsules. The highest steady-state C_{max} of itraconazole (1.7 mcg/mL) following administration of TOLSURA 130 mg BID seen in the studies conducted by the Applicant was observed to be lower than the highest C_{max} reported in the US labeling for SPORANOX (2 mcg/mL) when given at the dose of 200 mg BID. Given that the C_{max} of itraconazole following administration of TOLSURA is within the C_{max} reported following administration of SPORANOX, we can conclude that TOLSURA is likely to result in a similar safety profile as SPORANOX.

Does the population PK analysis support the proposed dosing regimens for TOLSURA 65 mg capsules in terms of comparability of PK exposure (AUCss and Cmaxss) between TOLSURA and SPORANOX capsules?

Yes. The population PK analysis was conducted using oral pharmacokinetic data pooled from 12 Phase 1 single-and multi-dose randomized crossover design studies comparing SPORANOX with TOLSURA. Results from population PK analyses and individual PK studies indicate that the overall itraconazole exposure (AUC and C_{max}) following administration of TOLSURA was slightly higher than SPORANOX. In addition, the C_{max} of itraconazole after administration of TOLSURA was less than the highest C_{max} reported in the SPORANOX package insert.

With the final model, itraconazole concentrations were simulated for 1000 subjects in each of the dosing scenarios. Multiple dose simulations were performed for 15 days of continuous drug administration. As shown in Table below, in the single dose setting under fasted and fed conditions, the predicted itraconazole $AUC_{inf\ for}$ TOLSURA was 112.6% and 119.6% of SPORANOX, respectively; the predicted itraconazole C_{max} was 126.7% and 120.8% of SPORANOX under fasted and fed conditions, respectively. Food decreased itraconazole exposure with both products (**Error! Reference source not found.**). Overall, the population effect of food was to decrease the AUC_{inf} and AUC_{0-72} of itraconazole to 73-82% of that in the fasted state, and to decrease C_{max} to 57-64 % of that in the fasted state. This reduction in systemic exposure of

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itraconazole for both TOLSURA and SPORANOX with food is contrary to the approved labeling for SPORANOX which recommends SPORANOX to be given with food to enhance oral bioavailability.

In the repeat dose settings, the differences between the products were greater since itraconazole exhibits non-linear PK (Figure 2). The median AUC_{0-72} for TOLSURA was 154% and 131% of SPORANOX after once and twice daily administration of two capsules under fed conditions, respectively. The median C_{max} for TOLSURA was 139% and 124% of SPORANOX after once and twice daily administration of two capsules, respectively (Table 1 in OCP Appendices: Predicted Median Itraconazole Exposure after Single and Multi-dose of Sporanox and SUBA-itraconazole = Table 8 below).

The inter-subject variability in PK exposure was less for TOLSURA (CV% for AUC_{0-72} ~41%; C_{max} ~46%) than SPORANOX (CV% for AUC_{0-72} ~63%; C_{max} ~66%). This amounts to an approximate 30-35% reduction in exposure variability for TOLSURA compared to SPORANOX (Please refer to Question 2.4 below for details).

However, it is important to note that the exposure of itraconazole following administration of TOLSURA was within the exposure range of SPORANOX. Overall the slightly higher exposure with TOLSURA is unlikely to be a concern from a safety perspective.

Table 8. Predicted Median Itraconazole Exposure after Single and Repeat Doses of TOLSURA and SPORANOX Capsules

		TOLSURA 65 mg		SPORANOX 100 mg		% of SPORANOX	
		AUC_{inf} (ng-h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng-h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng-h/mL)	C_{max} (ng/mL)
Single Dose	Fed	750	43.6	627.1	36.1	119.6	120.8
	Fasted	962	75.9	854.5	59.9	112.6	126.7
	Fed/Fasted (%)	78.0	57.4	73.4	60.3		
Repeat-dose Two capsules	Fed (once daily)	12171*	411	7924	295.1	153.6*	139.2
	Fed (twice daily)	85658*	1615	65230	1307	131.3*	123.6

Note: The values in the table were estimated by simulation of 1000 subjects in each of the dosing scenarios using the final model

* value was for AUC_{0-72} on Day 15 after multi-dose.

Source: Adapted from Table 18 on page 104 and Table 19 on page 108 of Applicant's population PK report

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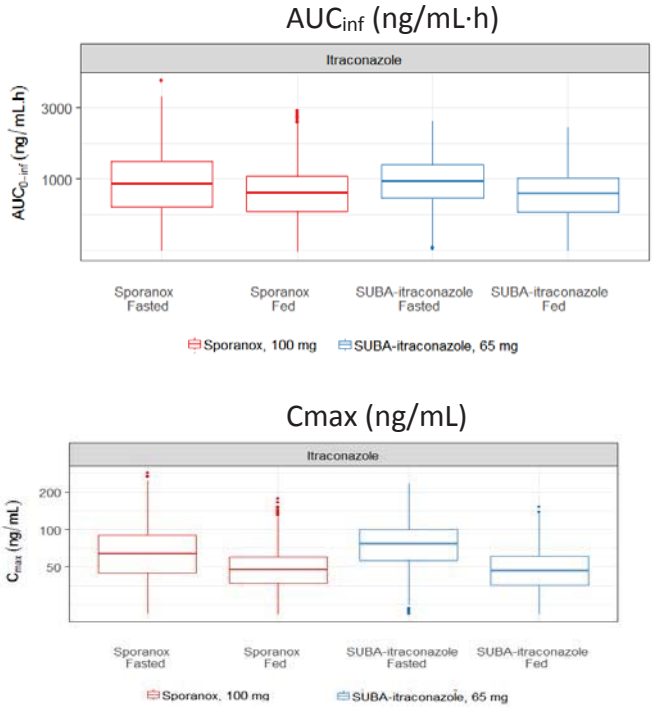
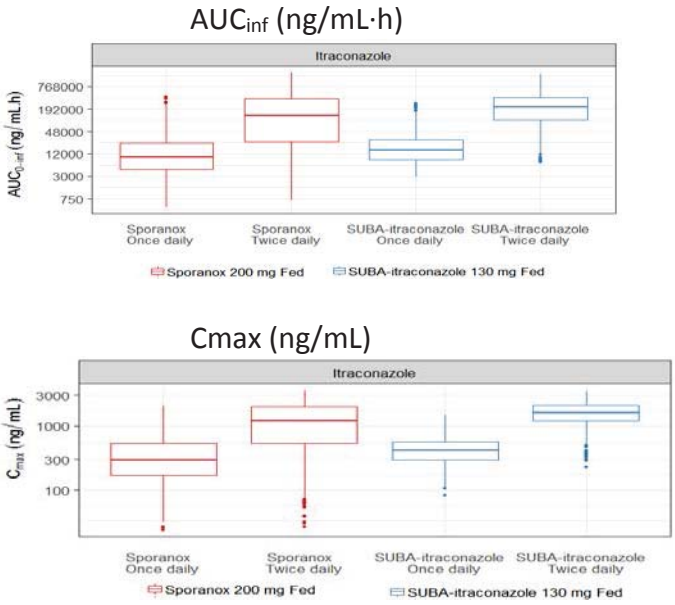
Figure 1: Predicted Itraconazole AUC_{inf} and C_{max} after Single Dose of SPORANOX and TOLSURA under Fed and Fasting Conditions



Source: Adapted from Figure 53 on page 102 of Applicant's population PK report

Figure 2: Predicted Itraconazole AUC_{inf} and C_{max} on Day 15 after Once-Daily and Twice-Daily Multiple Doses of 200 mg SPORANOX and 130 mg TOLSURA for 15 Days



Source: Adapted from Figure 55 on page 110 of Applicant's population PK report

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Model predicted itraconazole AUC_{inf} and C_{max} for once and twice daily dosing of 200 mg SPORANOX and 130 mg TOLSURA based on 1000 simulated subjects per dose

Is there an exposure-response relationship for TOLSURA from the studies conducted by the Applicant?

As expected, no exposure-response relationship for AEs was identified by the Applicant or the Clinical Pharmacology team based on data obtained from the healthy volunteer studies following multiple doses of TOLSURA. See the Appendix (Pharmacometrics Review) for additional details.

What is the effect of food on TOLSURA and SPORANOX capsules when given as single doses and at steady-state under fed vs. fasted conditions?

The effect of food on the BA of itraconazole upon administration TOLSURA capsules was evaluated in Study MPG009 and MPG017. The results for Study MPG009, an open-label, single-dose, crossover study designed to evaluate the comparative bioavailability of a single dose of TOLSURA 65 mg Capsule compared with a single dose of SPORANOX 100 mg Capsule in 52 healthy male and female subjects under fasted and fed conditions are presented below:

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Table 9. MPG009: Single dose TOLSURA capsules 65mg [1 X 65mg] vs. SPORANOX capsules 100mg [1 X 100mg] in healthy volunteers under fasted and fed conditions

Itraconazole (No of subjects completed = 52)							
Dose 65 mg or 100 mg *LS Geometric Means, Ratio of Means, and 90% Confidence Intervals*							
Parameter	*Contrast*	*Geometric Mean (CV)*	*N*	*Geometric Mean (CV)*	*N*	*Ratio (%)*	*90% C.I.*
Cmax	**A vs C**	101.6 (51)	51	62.8 (63)	52	161.8	141.4, 185.0
	B vs D	43.6 (75)	50	54.3 (61)	51	80.3	67.6, 95.3
	B vs A	43.6 (75)	50	101.6 (51)	51	42.9	36.6, 50.2
	D vs C	54.3 (61)	51	62.8 (63)	52	86.4	74.3, 100.4
	A vs D	101.6 (51)	51	54.3 (61)	51	187.2	164.2, 213.4
AUCt	**A vs C**	864.5 (55)	51	700.8 (66)	52	123.4	110.7, 137.5
	B vs D	564.4 (73)	50	625.7 (65)	51	90.2	78.2, 104.0
	B vs A	564.4 (73)	50	864.5 (55)	51	65.3	57.6, 74.0
	D vs C	625.7 (65)	51	700.8 (66)	52	89.3	78.6, 101.4
	A vs D	864.5 (55)	51	625.7 (65)	51	138.2	124.3, 153.5
AUC_{inf}	**A vs C**	901.3 (53)	51	734.2 (64)	52	122.8	109.7, 137.3
	B vs D	625.7 (51)	48	660.9 (61)	51	94.7	85.4, 105.0
	B vs A	625.7 (51)	48	901.3 (53)	51	69.4	63.8, 75.6
	D vs C	660.9 (61)	51	734.2 (64)	52	90.0	79.3, 102.1
	A vs D	901.3 (53)	51	660.9 (61)	51	136.4	122.9, 151.5

Treatment A: Fast: TOLSURA 65 mg capsules
Treatment B: Fed: TOLSURA 65 mg capsules
Treatment C: Fast: SPORANOX 100 mg capsules
Treatment D: Fed: SPORANOX 100 mg capsules
Source: Adapted from Applicant's Biopharm Summary

In Study MPG009, under fasted conditions, the mean AUC_{inf} and C_{max} of itraconazole following administration of single dose TOLSURA 65 mg were 23% and 62% higher, respectively, as compared to single dose SPORANOX 100 mg. Under fed conditions, the exposure of itraconazole following administration of TOLSURA was 5% lower (AUC_{inf}) and 19% lower (C_{max}) compared to SPORANOX.

Overall, food decreased the bioavailability of TOLSURA. The mean AUC_{inf} is 31% lower and the mean C_{max} is 57% lower when TOLSURA is administered after a high-fat, high calorie breakfast. The mean AUC_{inf} and C_{max} of itraconazole following administration of SPORANOX capsules were lower under fed conditions vs. fasted conditions. It is noteworthy that the approved labeling for SPORANOX capsules indicates that the oral BA of itraconazole is increased under fed conditions and the labeling recommends giving SPORANOX with food. The reason for this inconsistent result with SPORANOX in this study was not addressed by the Applicant and remains unknown.

Study MPG-017 was an open-label, multiple-dose, randomized, crossover, comparative bioavailability study performed in 24 healthy, adult, male and female subjects under fed and fasted conditions. This study compared the systemic exposure of itraconazole following administration of TOLSURA 130 mg (2 X 65mg) under fasted and fed (high fat FDA breakfast) conditions. The results are presented below:

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Table 10. MPG017: TOLSURA capsules 130 mg [2 X 65mg] administered under fed and fasted conditions in 24 healthy volunteers

LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Parameter	**Fed Mean ± SD**	**Fasted Mean ±SD**	**Fed/Fasted Ratio (%)**	**90% C.I.**
Cmax ss (ng/mL)	1403.1± 649.9	1920.7 ± 902.6	73.1	69.0, 77.3
Ctrough (ng/mL)	1008.7 ± 383.5	1102.1 ± 615.8	91.5	86.4, 97.0
AUCtau (ng-hr/mL)	13370.0 ± 5034.8	17122.2 ± 8044.3	78.1	74.5, 81.9

Source: Adapted from Applicant's Biopharm Summary

In Study MPG017, TOLSURA demonstrated a significant food effect. The systemic exposure, as given by the geometric mean ratios for AUC and C_{max} of itraconazole, were 22 % and 27% lower, respectively, when 130 mg (2 x 65 mg) was administered BID under fed conditions at steady-state, as compared to when the same dosage regimen was given under fasted conditions.

The results of this study, when taken together with the results of Study MPG009, indicate that the exposure of itraconazole was higher when TOLSURA was administered under fasted conditions vs. fed conditions. In addition, based on the fact the repeat dose studies that were conducted under fed conditions (per FDA recommendation) demonstrated that the steady-state systemic exposure to itraconazole following TOLSURA was comparable to that of SPORANOX. Thus, the labeling recommendations for TOLSURA will state that TOLSURA be administered with food.

What is the effect of co-administration of the proton pump inhibitor, omeprazole, on the PK of itraconazole following administration of TOLSURA capsules?

Study MPG016 was conducted to evaluate the effect of co-administration of 40 mg omeprazole QD for 7 days on the systemic exposure of itraconazole following TOLSURA administered as a single 130 mg dose (2 x 65 mg) under fasted conditions in 30 healthy subjects. The results are presented below in Table 11.

Table 11. MPG016: Single Dose TOLSURA capsules 130 mg [2 X 65mg] administered alone or with omeprazole 40 mg QD for 7 days under fasted conditions in healthy volunteers

LS Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Parameter	**Trt A Mean ± SD**	**Trt A+B Mean ± SD**	**Ratio of A+B/A**	**90% C.I.**
AUC_{∞} (ng·hr/mL)	2846.3 ±1644 .4	3477.9 ± 1572.6	122.2	108.7 to 137.3
C_{max} (ng/mL)	212.9 ± 119.1	278.8 ±106.8	130.9	111.4 to 153.8

Trt A: TOLSURA given alone
Trt B: TOLSURA given with omeprazole

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Source: Adapted from Applicant's Biopharm Summary

The study results indicate that there was an increase in the systemic exposure of itraconazole, in terms of both rate (C_{max} mean increase ~31%) and extent (AUC_{inf} mean increase ~22%) of absorption following co-administration of a single dose of 130 mg TOLSURA with 40 mg omeprazole dosed to steady-state. The 90% CIs for C_{max} and AUC_{inf} are both outside the 80% to 125% no effect boundary, indicating that there is a significant drug-drug interaction between omeprazole and TOLSURA. Furthermore, the magnitude of the upper bounds of the 90% CIs indicated that the increases in C_{max} and AUC_{inf} can be as high as 54% and 37%, respectively, if omeprazole is co-administered with TOLSURA. Of particular concern, in terms of safety, is the increase in the C_{max} of itraconazole. It is noteworthy that the magnitude of the increase in itraconazole C_{max} with co-administration of TOLSURA and omeprazole is with a single dose of TOLSURA and does not take into account the known non-linear PK and potential plasma accumulation of itraconazole following dosing of TOLSURA to steady-state. Thus, the labeling recommendation for TOLSURA capsules will include a cautionary statement regarding coadministered omeprazole with TOLSURA.

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7 Statistical and Clinical Evaluation

For this 505(b)(2) NDA the Applicant is relying on the Agency's findings of safety and effectiveness of the RLD, Sporanox (itraconazole) 100 mg capsules (NDA 20-083). No additional clinical trials were conducted for the proposed indications. Since the Applicant has not conducted any new efficacy studies with their product and are relying solely on the Agency's finding of safety and effectiveness of Sporanox, to support the proposed indications, a statistical review of the safety and efficacy for the proposed product has not been conducted.

8 Clinical Microbiology Review

No new clinical microbiology data were submitted to this application. The Microbiology sub-sections of the package insert (12.1 and 12.4) have been updated by the Applicant in accordance to the 21st Century Cures Act and the current FDA guidance, "Microbiological Data for Systemic Antibacterial Drug Products-Development, Analysis and Presentation".

From a clinical microbiology perspective, the Application is approvable.

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9 Review of Safety

Since the approval of Sporanox® (itraconazole) in 1992, significant safety experience has been gained in the U.S. and worldwide. Itraconazole is a relatively well-tolerated antifungal drug and its range of adverse reactions is similar to the other azole antifungals. The adverse event profile of itraconazole is described in the approved labeling for the product. Common adverse reactions include nausea, diarrhea, abdominal pain, rash, and headache. Severe adverse reactions include hepatotoxicity, congestive heart failure, Stevens-Johnson syndrome and allergic reactions including anaphylaxis.

To support this 505(b)(2) NDA comparative bioavailability studies between TOLSURA 65 mg Capsules and the RLD were required by the Agency across the full dosing range for the RLD in healthy subjects, specifically in the following studies: (also see Table 12 below.)

- 2 capsules three times a day for three days (Study MPG013)
- 2 capsules once a day, dosed to steady state (Study MPG012)
- 2 capsules twice a day, dosed to steady state (Study MPG015)
- Furthermore, to support the proposed labeling, the Applicant also conducted a food effect study dosing to steady state (Study MPG017) and a drug-drug interaction study to investigate the impact of co-administration of omeprazole on the bioavailability of TOLSURA 65 mg Capsules (Study MPG016).

Table 12: Bioavailability/Pharmacokinetic Studies Conducted in this NDA

Study Number (Region/RLD)	N	Dates	Dose (SUBA- itraconazole)	Dose (Sporanox®)	Fed/Fasted	Single dose or Multi-dose
MPG017 (USA/USA)	24	July-Sept 2017	2 x 65 mg	-	Fed and fasting	Once daily for 14 days
MPG016 (USA/USA)	30	July-Aug 2017	2 x 65 mg	-	Fasted	Once daily, with 7 days of omeprazole during Period II
MPG015 (USA/USA)	24	July-Aug 2017	2 x 65 mg	2 x 100mg	Fed	Twice daily for 14 days
MPG013 (USA/USA)	16	Jan– Apr 2017	2 x 65 mg	2 x 100mg	Fed	Three times daily for 3 days
MPG012 (USA/USA)	24	Dec 2015 - Feb 2016	2 x 65 mg	2 x 100mg	Fed	One daily for 14 days
MPG009 (USA/USA)	52	May-June 2013	1 x 65 mg	1 x 100 mg	Fed and fasting	Single dose

Reviewer's Comment: Study MPG009 was conducted with a single dose of SUBA -itraconazole 65 mg capsules and Sporanox 100 mg capsules under fed and fasting conditions, designed to evaluate the comparative bioavailability between the test drug and RLD and could provide additional safety data for this application. The brief description of the individual studies taken

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from the Applicant's complete study reports is provided below. The reviewer accepted the Applicant's safety data for these studies in healthy subjects. Safety analysis of the BA/PK studies was not integrated because of the varied study designs. A brief safety review of relevant literature for itraconazole (specifically for use of high daily doses of 400 mg and 600 mg in the treatment of severe systemic fungal infections) was performed by the reviewer to provide additional safety data.

9.1 Safety Review Approach

The adverse reactions reported in these BA/PK studies were experienced by healthy subjects.

9.1.1 Review of the Safety Database

Overall Exposure

In total, the number of healthy subjects exposed to SUBA -itraconazole in the 6 studies listed in Table 1 was 170. The demographic characteristics as shown in the Table 13 below are listed by race, gender, age group, weight, and BMI:

Table 13: Demographic Characteristics

		All	
		N	%
Race (%)	AMERICAN INDIAN OR ALASKA NATIVE	5	2.94
	ASIAN	18	10.59
	BLACK OR AFRICAN AMERICAN	78	45.88
	MULTI-RACIAL	2	1.18
	MULTIPLE	3	1.76
	WHITE	64	37.65
Gender (%)	Female	69	40.59
	Male	101	59.41
Age Group (%)	39 or less	99	58.24
	40-64	70	41.18
	65 & older	1	0.59
BMI	Mean	26.4	
	SD	2.99	
	Median	26.7	
	Range	20.3 - 30	
Weight (KG)	Mean	80.77	
	SD	12.44	
	Median	80.74	
	Range	59.4 -110.7	
	All	170	100.00

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Relevant characteristics of the safety population

The majority of reported adverse events were mild to moderate in severity and typical of those generally observed following the administration of Sporanox. Overall the study drug was well tolerated. The age range of the healthy subjects in the studies were from 19 to 67 years. There were more male than female subjects enrolled and more subjects were African-American.

Adequacy of the safety database:

The overall number of healthy subjects exposed to SUBA-itraconazole 65 mg capsules in these BA/PK studies (n=170) appears adequate to perform a safety evaluation.

9.1.2 Safety Results

Deaths

No deaths were reported in the studies.

Serious Adverse Events

No serious AEs were reported in the studies.

Dropouts and/or Discontinuations Due to Adverse Reactions

Two subjects dropped-out from Study MPG0012 due to adverse reactions:

- Subject No (b) (6) (SUBA-itraconazole arm) dropped out from the study due to an AE (hives on both hands and arms up to elbow, possibly drug-related) in Period 1.
- Subject No (b) (6) (Sporanox® arm) dropped out from the study due to an AE (hives on both hands and arms up to elbow; and later hives on chest, back, shoulders, abdomen, thighs, and both knees, possibly drug-related) in Period 1.

One subject (Subject No (b) (6)) (SUBA-itraconazole arm) dropped out from Study MPG0015 due to tooth pain (deemed not drug-related).

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Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse reactions reported in the individual clinical studies are briefly summarized below.

1. Study MPG009

This study was designed to evaluate the comparative bioavailability 1 x SUBA-itraconazole 65 mg capsules compared with 1 x Sporanox 100 mg capsules in healthy male and female subjects under fasted and fed conditions. The study was conducted in 52 subjects, of whom 50 completed the study. The following subjects did not complete all periods of the study:

- Subject (b) (6) completed period 1 of the study, receiving treatment C.
- Subject (b) (6) completed periods 1, 2, and 3, receiving treatments D, C, and A, respectively.

Both subjects completed at least one period of the study and are included in the final analyses.

A summary of the adverse events reported to be drug related is provided below in Table 14.

Table 14: Study MPG009-Incidence of Treatment Emergent Adverse Events

	Incidence by Treatment Group			
System Organ Class Term Preferred Term	**SUBA N = 51**	**SUBA N = 50**	**Sporanox N = 52**	**Sporanox N = 51**
Cardiac disorders				
Bradycardia	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)
Tachycardia	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)
Eye disorders				
Eye pruritus	0 (0%)	1 (2.0%)	0 (0%)	0 (0%)
Gastrointestinal disorders				
Abdominal pain upper	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)
Investigations				
Alanine aminotransferase increased	2 (3.9%)	1 (2.0%)	0 (0%)	0 (0%)
Aspartate aminotransferase increased	0 (0%)	0 (0%)	2 (3.8%)	1 (2.0%)
Blood albumin increased	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)
Blood bilirubin increased	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)
Blood creatinine increased	0 (0%)	0 (0%)	0 (0%)	1 (2.0%)
Gamma-glutamyltransferase increased	0 (0%)	0 (0%)	2 (3.8%)	1 (2.0%)
Neutrophil count decreased	2 (3.9%)	2 (4.0%)	1 (1.9%)	0 (0%)
White blood cell count decreased	2 (3.9%)	2 (4.0%)	2 (3.8%)	0 (0%)
Metabolism and nutrition				

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	Incidence by Treatment Group			
System Organ Class Term Preferred Term	SUBA N = 51	SUBA N = 50	Sporanox N = 52	Sporanox N = 51
disorders				
Increased appetite	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders				
Dizziness	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)
Headache	3 (5.9%)	1 (2.0%)	3 (5.8%)	1 (2.0%)
Migraine	0 (0%)	1 (2.0%)	0 (0%)	0 (0%)
Somnolence	3 (5.9%)	3 (6.0%)	5 (9.6%)	4 (7.8%)
Vascular disorders				
Hypotension	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)

Source: Applicant's Study Report and Datasets for Study MPG009

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Trt A = SUBA™-itraconazole 65 mg Capsules fasted state
Trt B = SUBA™-itraconazole 65 mg Capsules fed state
Trt C = Sporanox® 100 mg Capsules fasted state
Trt D = Sporanox® 100 mg Capsules fed state

2. Study MPG012

Table 15: Study MPG012-Incidence of Treatment Emergent Adverse Events

	Reported Incidence by Treatment Groups (%)	
Body system/adverse event	SUBA N=23	SPORANOX N= 23
Nervous system disorders		
Headache	02 (8.7%)	01 (4.3%)
Enhanced sense of smell	01 (4.3%)	NA
Gastrointestinal disorders		
Dry mouth	01 (4.3%)	NA
Nausea	02 (8.7%)	NA
Light colored stools	01 (4.3%)	NA
Difficult bowel movements	01 (4.3%)	NA
Upset stomach	NA	01 (4.3%)
Skin and subcutaneous tissue disorders		
Hives on both hands and arms up to elbow	01 (4.3%)	01 (4.3%)
Hives on back	01 (4.3%)	NA
Hives on both legs	01 (4.3%)	NA
Hives on stomach	01 (4.3%)	NA
Hives on chest	01 (4.3%)	NA
Bad body odor	01 (4.3%)	NA
Dry skin (entire body)	01 (4.3%)	NA
Itchy skin (entire body)	01 (4.3%)	NA
Rash on right antecubital space	01 (4.3%)	NA
Upper left forearm laceration	NA	01 (4.3%)
Left cheek laceration	NA	01 (4.3%)
Hives on chest, back, shoulders, abdomen, thighs and	NA	01 (4.3%)

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Reported Incidence by Treatment Groups (%)		
Body system/adverse event	**SUBA N=23**	**SPORANOX N= 23**
knees		
Dry skin (Both arms)	NA	01 (4.3%)
Respiratory, thoracic and mediastinal disorders		
Sinus congestion	01 (4.3%)	NA
General disorders and administration site conditions		
Loss of appetite	NA	01 (4.3%)
Total	**18 (78.3%)**	**08 (34.8%)**

Source: Applicant's Study Report and Datasets for Study MPG012. N=Number of subjects dosed for each treatment
n=Number of subjects reporting at least one incidence of respective adverse event
(%)= percentage of subjects reporting at least one incidence of respective adverse event
NOTE: During the entire duration of the study 23 subjects were exposed to Test (T) and 23 subjects were exposed to Reference (R) treatment.

Study started with twenty-four (24) subjects and twenty-one (21) subjects completed the study.

No serious adverse events were reported. Over all twenty-six (26) adverse events were reported in eleven (11) subjects in entire duration of the study. Subject No. (b) (6) and No. (b) (6) were dropped from the study due to adverse event in Period-I. Subject No. (b) (6) was dropped from trial due to protocol non-compliance in Period-II.

3. Study MPG013

The objective of this Study MPG013 was to evaluate the comparative bioavailability between SUBA-itraconazole 65 mg Capsules and Sporanox (itraconazole) 100 mg Capsules following multiple-dose administration in healthy, adult, non-smoking subjects, under fed conditions.

A total of 16 subjects started the study, with 15 subjects (8 female, 7 male) completing the study. The study subjects were healthy, adult, non-smoking male and female subjects from 18 to 55 years of age and a body mass index (BMI) ≥18.0 and ≤ 33.0 kg/m2 were enrolled in this study from the community at large. The study populations were consistent with requirements for comparative bioequivalence testing. In each period, subjects were administered two capsules of SUBA-itraconazole 65 mg Capsules or Sporanox (itraconazole) 100 mg Capsules three times daily (8 hours apart) on Days 1-3 and once on Day 4 under fed conditions. The treatment phases were separated by a washout of 21 days.

The study drugs were well-tolerated by the subjects participating in this study. Overall, there were 10 TEAEs affecting 4 subjects, of which one was treatment-related. All reported TEAEs were mild in severity and resolved prior to the end of the study. No subject discontinued from the study due to a TEAE. No serious adverse events (SAEs) were reported in the study.

Reference ID: 4360457

Table 16: Study MPG013-Incidence of Treatment Emergent Adverse Events

	Reported Incidence by Treatment Group N (%)		
System Organ Class Term Preferred Term	**SUBA N = 15**	**SPORANOX N = 16**	**Total N = 16**
Subjects with One or More TEAEs	**3 (20.0%)**	**2 (12.5%)**	**4 (25.0%)**
Subjects with No TEAEs	12 (80.0%)	14 (87.5%)	12 (75.0%)
Gastrointestinal disorders	**2 (13.3%)**	**1 (6.3%)**	**3 (18.8%)**
Abdominal pain	1 (6.7%)	0 (0%)	1 (6.3%)
Nausea	1 (6.7%)	0 (0%)	1 (6.3%)
Toothache	0 (0%)	1 (6.3%)	1 (6.3%)
General disorders and administration site conditions	**0 (0%)**	**1 (6.3%)**	**1 (6.3%)**
Pyrexia	0 (0%)	1 (6.3%)	1 (6.3%)
Investigations	**1 (6.7%)**	**0 (0%)**	**1 (6.3%)**
Platelet count decreased	1 (6.7%)	0 (0%)	1 (6.3%)
Nervous system disorders	**0 (0%)**	**1 (6.3%)**	**1 (6.3%)**
Headache	0 (0%)	1 (6.3%)	1 (6.3%)
Reproductive system and breast disorders	**0 (0%)**	**1 (6.3%)**	**1 (6.3%)**
Dysmenorrhoea	0 (0%)	1 (6.3%)	1 (6.3%)
Respiratory, thoracic and mediastinal disorders	**0 (0%)**	**1 (6.3%)**	**1 (6.3%)**
Epistaxis	**10 (0%)**	**1 (6.3%)**	1 (6.3%)

Source: Applicant's Study Report and Datasets for Study MPG013.

4. Study MPG015

A total of 24 subjects started the study, with 16 subjects completing the study; 20 subjects (9 female and 11 male) contributed data to the Treatment A arm, 22 subjects (9 female, 13 male) to Treatment B. In each period, subjects were confined to the clinical facility from 10.5 hours prior to dosing until after the 24-hour post-dose blood draw on Day 15. In each period, subjects were administered two capsules of SUBA-itraconazole 65 mg Capsules or Sporanox (itraconazole) 100 mg Capsules twice daily (12 hours apart) on Days 1-14 and once on Day 15 under fed conditions. The treatment phases were separated by a washout of 14 days between the Day 15 drug administration in Period 1 and the Day 1 drug administration in Period 2. Treatment emergent adverse events (TEAE) from the study are listed below in Table 17.

Table 17: Study MPG015- Incidence of Treatment Emergent Adverse Events

	Reported Incidence by Treatment Group N (%)		
System Organ Class Term Preferred Term	**SUBA N = 20**	**SPORANOX N = 22**	**Total N = 24**
Subjects with One or More TEAEs	**9 (45.0%)**	**4 (18.2%)**	**11 (45.8%)**
Subjects with No TEAEs	11 (55.0%)	18 (81.8%)	13 (54.2%)
Gastrointestinal disorders	**5 (25.0%)**	**1 (4.5%)**	**5 (20.8%)**
Abdominal pain	1 (5.0%)	0 (0%)	1 (4.2%)
Abdominal pain upper	1 (5.0%)	1 (4.5%)	2 (8.3%)
Abdominal tenderness	1 (5.0%)	0 (0%)	1 (4.2%)
Constipation	1 (5.0%)	0 (0%)	1 (4.2%)
Nausea	3 (15.0%)	0 (0%)	3 (12.5%)

Reference ID: 4360457

	Reported Incidence by Treatment Group N (%)		
System Organ Class Term Preferred Term	**SUBA N = 20**	**SPORANOX N = 22**	**Total N = 24**
Toothache	1 (5.0%)	0 (0%)	1 (4.2%)
Injury, poisoning and procedural complications	**1 (5.0%)**	**0 (0%)**	**1 (4.2%)**
Arthropod bite	1 (5.0%)	0 (0%)	1 (4.2%)
Investigations	**0 (0%)**	**2 (9.1%)**	**2 (8.3%)**
Alanine aminotransferase increased	0 (0%)	1 (4.5%)	1 (4.2%)
Neutrophil count increased	0 (0%)	1 (4.5%)	1 (4.2%)
White blood cell count increased	0 (0%)	1 (4.5%)	1 (4.2%)
Musculoskeletal and connective tissue disorders	**1 (5.0%)**	**1 (4.5%)**	**2 (8.3%)**
Back pain	1 (5.0%)	0 (0%)	1 (4.2%)
Neck pain	0 (0%)	1 (4.5%)	1 (4.2%)
Nervous system disorders	**4 (20.0%)**	**1 (4.5%)**	**5 (20.8%)**
Dizziness	1 (5.0%)	1 (4.5%)	2 (8.3%)
Headache	3 (15.0%)	0 (0%)	3 (12.5%)
Reproductive system and breast disorders	**0 (0%)**	**2 (9.1%)**	**2 (8.3%)**
Dysmenorrhoea	0 (0%)	2 (9.1%)	1 (8.3%)

Source: Applicant's Study Report and Datasets for Study MPG015.

5. Study MPG016

The primary objective of the study was to evaluate the effect of multiple daily oral doses (steady-state conditions) of omeprazole delayed-release capsules on the pharmacokinetics of SUBA-itraconazole capsules after a single oral dose in healthy, adult male and female subjects under fasted conditions.

A total of 30 subjects started the study, with 28 subjects (23 male, 5 female) completing the study. There was a 14-day washout interval between Treatment A dosing on Day 1 in each study period.

Treatment emergent adverse events (TEAE) all causalities from the study are listed below in Table 18.

Table 18: Study MPG016- Incidence of Treatment Emergent Adverse Events

	Reported Incidence by Treatment Groups		
Body System/Adverse Event	**Fasted Bioequivalence Study**		
	SUBA N (%)	**Omeprazole N (%)**	**SUBA+Omeprazole N (%)**
Gastrointestinal disorders			
Abdominal pain	0 (0.0%)	0 (0.0%)	1 (3.6%)
Dry mouth	1 (3.3%)	0 (0.0%)	1 (3.6%)
Dyspepsia	1 (3.3%)	0 (0.0%)	0 (0.0%)
Flatulence	0 (0.0%)	1 (3.3%)	0 (0.0%)
Nausea	0 (0.0%)	0 (0.0%)	1 (3.6%)
Vomiting	0 (0.0%)	0 (0.0%)	1 (3.6%)

Reference ID: 4360457

Body System/Adverse Event	Reported Incidence by Treatment Groups		
	Fasted Bioequivalence Study		
	SUBA N (%)	Omeprazole N (%)	SUBA+Omeprazole N (%)
General disorders and administration site conditions			
Asthenia	0 (0.0%)	0 (0.0%)	1 (3.6%)
Pain	0 (0.0%)	1 (3.3%)	0 (0.0%)
Swelling	0 (0.0%)	1 (3.3%)	0 (0.0%)
Infections and infestations			
Vaginal infection	0 (0.0%)	0 (0.0%)	1 (3.6%)
Injury, poisoning and procedural complications			
Contusion	0 (0.0%)	1 (3.3%)	0 (0.0%)
Laceration	0 (0.0%)	1 (3.3%)	0 (0.0%)
Skin abrasion	1 (3.3%)	1 (3.3%)	0 (0.0%)
Investigations			
Hepatic enzyme increased	1 (3.3%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders			
Decreased appetite	2 (6.7%)	0 (0.0%)	0 (0.0%)
Nervous system disorders			
Headache	1 (3.3%)	1 (3.3%)	0 (0.0%)
Psychiatric disorders			
Insomnia	1 (3.3%)	0 (0.0%)	0 (0.0%)
TOTAL N (%)	5 (16.7%)	4 (13.3%)	2 (7.1%)

Source: Applicant's Study Report and Datasets for Study MPG016

N% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) x 100.

Total N%= (Number of subjects that reported at least one AE / number of subjects dosed with respective study drug) x 100. Treatment A (Test) = 30 subjects dosed. Treatment B = 30 subjects dosed. Treatment A+B (Test + omeprazole) = 28 subjects dosed.

6. Study MPG017

A total of 24 subjects started the study, with 20 subjects (3 Female, 20 male) completing the study. In each period, subjects were confined to the clinical facility from 10.5 hours prior to dosing until after the 24-hour post-dose blood draw on Day 15.

In each period, subjects were administered two capsules of SUBA-itraconazole 65 mg Capsules twice daily (12 hours apart) on Days 1-14 and once on Day 15 under fasted or fed conditions. The treatment phases were separated by a washout of 14 days between the Day 15 drug administration in Period 1 and the Day 1 drug administration in Period 2.

Treatment emergent adverse events (TEAE) from the study are listed below in Table 19.

Table 19: Study MPG017- Incidence of Treatment Emergent Adverse Events

	Reported Incidence by Treatment Group N (%)		
System Organ Class Term Preferred Term	SUBA N = 23	SPORANOX N = 21	Total N = 24
Subjects with One or More TEAEs	**11 (47.8%)**	**6 (28.6%)**	**14 (58.3%)**

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System Organ Class Term Preferred Term	Reported Incidence by Treatment Group N (%)		
	SUBA N = 23	SPORANOX N = 21	Total N = 24
Subjects with No TEAEs	12 (52.2%)	15 (71.4%)	10 (41.7%)
Cardiac disorders	**1 (4.3%)**	**0 (0%)**	**1 (4.2%)**
Palpitations	1 (4.3%)	0 (0%)	1 (4.2%)
Eye disorders	**0 (0%)**	**1 (4.8%)**	**1 (4.2%)**
Eye irritation	0 (0%)	1 (4.8%)	1 (4.2%)
Gastrointestinal disorders	**3 (13.0%)**	**2 (9.5%)**	**4 (16.7%)**
Constipation	1 (4.3%)	2 (9.5%)	2 (8.3%)
Diarrhoea	1 (4.3%)	0 (0%)	1 (4.2%)
Nausea	1 (4.3%)	0 (0%)	1 (4.2%)
General disorders and administration site conditions	**2 (8.7%)**	**1 (4.8%)**	**3 (12.5%)**
Chest pain	2 (8.7%)	0 (0%)	2 (8.3%)
Fatigue	0 (0%)	1 (4.8%)	1 (4.2%)
Injury, poisoning and procedural complications	**2 (8.7%)**	**0 (0%)**	**2 (8.3%)**
Thermal burn	1 (4.3%)	0 (0%)	1 (4.2%)
Tooth fracture	1 (4.3%)	0 (0%)	1 (4.2%)
Investigations	**0 (0%)**	**2 (9.5%)**	**2 (8.3%)**
Eosinophil count increased	0 (0%)	1 (4.8%)	1 (4.2%)
Urine analysis abnormal	0 (0%)	1 (4.8%)	1 (4.2%)
Musculoskeletal and connective tissue disorders	**2 (8.7%)**	**1 (4.8%)**	**3 (12.5%)**
Back pain	0 (0%)	1 (4.8%)	1 (4.2%)
Musculoskeletal stiffness	1 (4.3%)	0 (0%)	1 (4.2%)
Neck pain	1 (4.3%)	0 (0%)	1 (4.2%)
Pain in extremity	0 (0%)	1 (4.8%)	1 (4.2%)
Nervous system disorders	**2 (8.7%)**	**0 (0%)**	**2 (8.3%)**
Headache	1 (4.3%)	0 (0%)	1 (4.2%)
Hypoaesthesia	1 (4.3%)	0 (0%)	1 (4.2%)
Renal and urinary disorders	**1 (4.3%)**	**0 (0%)**	**1 (4.2%)**
Urine odour abnormal	1 (4.3%)	0 (0%)	1 (4.2%)
Reproductive system and breast disorders	**0 (0%)**	**1 (4.8%)**	**1 (4.2%)**
Dysmenorrhoea	0 (0%)	1 (4.8%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	**2 (8.7%)**	**0 (0%)**	**2 (8.3%)**
Cough	1 (4.3%)	0 (0%)	1 (4.2%)

Source: Applicant's Study Report and Datasets for Study MPG017.

Laboratory Findings

A small number of mild liver enzyme elevations was noted in Study MPG009, Study MPG013, MPG016, and MPG017 for both SUBA -itraconazole and the Sporanox arms during drug administration but reversed to normal baseline values after the study periods. No other clinically significant findings in clinical laboratory evaluations in the studies.

Vital Signs

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No safety-related vital signs were reported.

Electrocardiograms (ECGs) and QT

No abnormal ECG and QT findings were reported. All the studies collected ECGs.

Immunogenicity

Not applicable.

9.1.3 Analysis of Submission-Specific Safety Issues

No specific safety issue was reported in the studies for healthy subjects. No specific safety concerns were identified in all demographic subgroups.

9.2 Integrated Assessment of Safety

The safety assessment for TOLSURA™ 65 mg capsules is summarized in the review of the individual BA/PK studies. The safety data in these studies are small which is expected for a BA/PK studies in healthy subjects. The adverse reactions experienced by the subjects in the TOLSURA arm were similar to the RLD, Sporanox 100 mg capsules and commonly related to the gastrointestinal system disorders, central nervous system, and skin disorders.

Additionally, to garner safety data of itraconazole in the high dosing exposure for the treatment of severe systemic fungal infections, a review of the scientific literature was conducted. The reviewer performed a brief safety review of the literature for itraconazole using doses of 400 mg and 600 mg administered orally for the treatment of severe systemic fungal infections. PubMed was searched for relevant publications reporting adverse events associated with use of high dose itraconazole (400 mg and 600 mg) from 1991 up to the present. Only articles that provided safety information for oral itraconazole (400 mg and 600 mg) were included in this review.

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Literature Review of Case Reports of Systemic Fungal Mycoses treated with Oral Itraconazole 400 mg and 600 mg

Table 20: Summary of Case Reports

Author of Literature article/# Patients	Type of Mycoses/ Site of Disease	Daily Itraconazole dose (mg)	Duration of therapy (months)	Outcome	Authors Comment/ Adverse Events
Denning DW, et al	Invasive Aspergillosis				
# 1	Thoracic spine	400 mg	12	+Response	Cultures negative after 4 mos. of itraconazole
# 2	Lung	400 mg	3.5	+Response	Died of CLL with no evident fungal disease
# 3	Lung	400 mg	12	+Response	Switched from Ampho B because of toxicity
# 4	Sinuses and carotid artery	400 mg	1.5	No response	Ampho B failed before itraconazole was given. Patient was obtunded. Itraconazole given with difficulty; low serum concentration. Patient died. Patient had GI bleed due to erosive esophagitis.
# 5	Lung	400 mg	1	Failed	Died. Endocarditis at autopsy

Reference ID: 4360457

Table 20: Case Reports (continued)

Author of Literature article/# Patients	Type of Mycoses/Site of Disease	Daily Itraconazole dose (mg)	Duration of therapy (months)	Outcome	Authors Comment/Adverse Events
# 6	Liver and spleen	400 mg	12	+Response	Amphotericin B failed before itraconazole was given. Ankle edema was noted after 2 weeks of itraconazole.
# 7	Lung	400 mg	5.5	+Response	No toxicity
# 8	Pleura	400 mg	6	+Response	No AEs reported.
# 9	Sphenoid sinus/ Pterigomaxillary space	400 mg	4	+Response	No AEs reported Surgery possibly contributed to response
# 10	Pericardium	400 mg	6	+Response	Pericardiectomy removed part of disease
# 11	Mastoid	400 mg	2	+Response	Mastoidectomy possibly contributed to response
# 12	Right knee	400 mg	12	Recurrence of inflammation	Clinical response, cultures negative. Three months after therapy was completed, inflammation of joint recurred. Patient refused arthrocentesis.

Reference ID: 4360457

Table 20: Case Reports (continued)

Author of Literature article/# Patients	Type of Mycoses/ Site of Disease	Daily Itraconazole dose (mg)	Duration of therapy (months)	Outcome	Authors Comment
Sharkey et al (High-dose Itraconazole in the Treatment of Systemic Mycoses)					
#1 25 yo M	Phaeohyphomycosis (sinus; soft tissue, bone; optic nerve; brain)	600 mg	8	Stabilization	Sinus pain and headache resolved; abnormalities seen in CT scans stabilized; patient remained stable after 3 yr of ITZ now on reduced dose of 400 mg/day.
#2 32 yo M	Phaeohyphomycosis (sinus; soft tissue, palpebral junction, bone)		16	Good response	Improvement in symptom and abnormalities seen in CT scans with ITZ at 600 mg/day; with subsequent therapy at 400 mg/day, symptoms resolved and abnormalities seen in CT scans stabilized; ITZ discontinued after 3 yr with no evidence of recurrence at a 3-mo follow-up
#3 24 yo M	Coccidioidomycosis; soft tissue, lymph nodes, laryngeal structures	600 mg	4	Resolution of symptoms	Patient remained stable, with negative cultures and chronic epiglottal swelling, with ITZ at 600 mg/day, with a reduction to 400 mg/day at the request of the manufacturer; completed 5 yr of ITZ at 400 mg/day; continued on maintenance therapy with FLU following closure of study by manufacturer.

Reference ID: 4360457

Author of Literature article/# Patients	Type of Mycoses/ Site of Disease	Daily Itraconazole dose (mg)	Duration of therapy (months)	Outcome	Authors Comment
#4 39 yo M	Coccidioidomycosis; soft tissue, lymph nodes, lungs, bone	600 mg	3	Resolution of symptoms	Resolution of symptoms and lymphadenopathy prior to dose reduction to 400 mg/day; completed 1 yr of ITZ; relapsed 1.5 yr after completion but responded to re-institution of ITZ.
#5 27 yo M	Coccidioidomycosis; lungs	600 mg	3	Resolution of symptoms	Symptoms resolved with ITZ 600 mg/day, but dose was reduced to 400 mg/day at the request of manufacturer; completed 6 mo of ITZ with no evidence of relapse at a 6 mo follow-up.
#6 23yo M	Cryptococcosis (AIDS related); meninges, bone marrow, lymph nodes	400 mg	4	No response	Progression of symptoms with positive cultures
#7 18 yo M	Cryptococcosis (AIDS related); meninges, brain (encephalitis)	400 mg	3	No response	Progression of symptoms and signs with rising latex cryptococcal antigen test (LCAT) but negative cultures.
#8 18 yo M	Coccidioidomycosis; lungs, pleura	400 mg	3	Initial improvement of symptoms and signs; then failure	Improvement of symptoms and signs, but dose was reduced after development of toxicity (hypoadrenalism); persistence of symptoms, radiographic abnormalities, and positive cultures after 10 mo of ITZ at 400 mg/day.

Le et al report[1] the results from an open-label, noninferiority trial of 440 HIV-infected adults with talaromycosis, confirmed by either microscopy or culture, randomized to receive either intravenous amphotericin B deoxycholate (amphotericin) (219 patients), at a dose of 0.7 to 1.0 mg per kilogram of body weight per day, or itraconazole capsules (221 patients), at a dose of 600 mg per day for 3 days, followed by 400 mg per day, for 11 days; thereafter, all the patients received maintenance therapy with itraconazole.

Reviewer's Comment: Please note that the table below is provided in the article. The clinical reviewer made minor formatting changes to the table.

Table 21: Summary of Clinical Grade 3 and 4 adverse events until 24 weeks

Event	Amphotericin B (n=217)	Itraconazole (n=218)	P value
Any event			
At least one adverse event – no. of patients (%)	119 (54.84)	110 (50.46)	0.39
No. of adverse events	180	160	0.27
T. marneffei complications – no. of patients (%)	19 (8.76)	57 (26.15)	<0.0001
Respiratory failure	10 (4.61)	12 (5.50)	0.83
T. marneffei relapse	3 (1.38)	15 (6.88)	0.006
T. marneffei poor treatment response	1 (0.46)	13 (5.96)	0.002
T. marneffei IRIS	0 (0.00)	14 (6.42)	<0.0001
Wasting syndrome due to *T. marneffei*	5 (2.30)	6 (2.75)	1.00
Allergic and immune disorders – no. of patients (%)	52 (23.96)	3 (1.38)	<0.0001
Infusion reaction	49 (22.58)	1 (0.46)	<0.0001
Skin rash	1 (0.46)	1 (0.46)	1.00
Drug-induced hepatitis	1 (0.46)	0 (0.00)	0.50
Drug-related hemolytic anemia	1 (0.46)	0 (0.00)	0.50
Hives (platelet transfusion)	0 (0.00)	1 (0.46)	1.00
Skin rash (suspect due to cotrimoxazole)	1 (0.46)	0 (0.00)	0.50
Skin rash (suspect due to itraconazole)	1 (0.46)	0 (0.00)	0.50
AIDS-associated stage IV diseases – no. of patients (%)	19 (8.76)	22 (10.09)	0.74
Extrapulmonary TB	7 (3.23)	5 (2.29)	0.58
Wasting syndrome due to HIV	4 (1.84)	4 (1.83)	1.00
Disseminated TB	3 (1.38)	5 (2.29)	0.72
CMV retinitis	3 (1.38)	4 (1.83)	1.00
PCP	2 (0.92)	4 (1.83)	0.69
Toxoplasmosis	0 (0.00)	2 (0.92)	0.50
CMV polyneuritis	1 (0.46)	0 (0.00)	0.50
Disseminated MAC infection	0 (0.00)	1 (0.46)	1.00
AIDS-associated stage III diseases – no. of patients (%)	21 (9.68)	23 (10.55)	0.87
Pulmonary TB	19 (8.76)	22 (10.09)	0.74
Oral herpes	2 (0.92)	0 (0.00)	0.25

[1] Le et al: A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis N Engl J Med. 2017 Jun 15;376(24):2329-2340. doi: 10.1056/NEJMoa1613306.

Reference ID: 4360457

Event	Amphotericin B (n=217)	Itraconazole (n=218)	P value
Abdominal lymphadenitis	0 (0.00)	1 (0.46)	1.00
TB IRIS	0 (0.00)	1 (0.46)	1.00
Other infections – no. of patients (%)	12 (5.53)	19 (8.72)	0.26
Pneumonia	6 (2.76)	6 (2.75)	1.00
Sepsis (*Salmonella* spp.)	0 (0.00)	4 (1.83)	0.12
Suspect Parvovirus B19 infection	1 (0.46)	1 (0.46)	1.00
Infectious diarrhea	1 (0.46)	1 (0.46)	1.00
Sepsis	1 (0.46)	1 (0.46)	1.00
Shock	2 (0.92)	0 (0.00)	0.25
Buttock abscess	1 (0.46)	0 (0.00)	0.50
Fever	0 (0.00)	1 (0.46)	1.00
Scabies	0 (0.00)	1 (0.46)	1.00
Sepsis (ESBL *Klebsiella pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Sepsis (*Streptococcus pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Urinary tract infection	0 (0.00)	1 (0.46)	1.00
Viral infection	0 (0.00)	1 (0.46)	1.00
Nutritional and metabolic disorders – no. of patients (%)	9 (4.15)	3 (1.38)	0.09
Hypokalemia	4 (1.84)	2 (0.92)	0.45
Hypomagnesemia	3 (1.38)	0 (0.00)	0.12
Anasarca	1 (0.46)	0 (0.00)	0.50
Fatigue	1 (0.46)	0 (0.00)	0.50
Hypocalcemia	0 (0.00)	1 (0.46)	1.00
Blood and lymphatic disorders – no. of patients (%)	16 (7.37)	3 (1.38)	0.002
Anemia	8 (3.69)	2 (0.92)	0.06
Neutropenia	2 (0.92)	0 (0.00)	0.25
Pancytopenia	1 (0.46)	1 (0.46)	1.00
Phlebitis	2 (0.92)	0 (0.00)	0.25
Thrombocytopenia	2 (0.92)	0 (0.00)	0.25
Epistaxis	1 (0.46)	0 (0.00)	0.50
Thrombophlebitis	1 (0.46)	0 (0.00)	0.50
Central nervous system (CNS) disorders – no. of patients (%)	1 (0.46)	3 (1.38)	0.62
Meningoencephalitis	1 (0.46)	1 (0.46)	1.00
CNS syndrome of unclear etiology	0 (0.00)	1 (0.46)	1.00
Encephalophathy	0 (0.00)	1 (0.46)	1.00
Cardiovascular disorders – no. of patients (%)	2 (0.92)	0 (0.00)	0.25
Hypotension	1 (0.46)	0 (0.00)	0.50
Stroke	1 (0.46)	0 (0.00)	0.50
Respiratory disorders– no. of patients (%)	2 (0.92)	1 (0.46)	0.62
Dyspnea	2 (0.92)	0 (0.00)	0.25
Hemoptysis	0 (0.00)	1 (0.46)	1.00
Gastrointestinal disorders – no. of patients (%)	8 (3.69)	10 (4.59)	0.81
Diarrhea	3 (1.38)	2 (0.92)	0.69
Gastrointestinal bleeding	2 (0.92)	3 (1.38)	1.00
Abdominal distention	1 (0.46)	1 (0.46)	1.00
Nausea/vomiting	1 (0.46)	1 (0.46)	1.00
Peritonitis	1 (0.46)	1 (0.46)	1.00
Esophageal stricture	0 (0.00)	1 (0.46)	1.00
Hepatitis – cholestasis	1 (0.46)	0 (0.00)	0.50

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Event	Amphotericin B (n=217)	Itraconazole (n=218)	P value
Suspect drug-induced liver failure	0 (0.00)	1 (0.46)	1.00
Renal disorders	10 (4.61)	1 (0.46)	0.006
Renal failure	10 (4.61)	1 (0.46)	0.006
Bone and joint disorders – no. of patients (%)	1 (0.46)	0 (0.00)	0.50
Acute gout	1 (0.46)	0 (0.00)	0.50
Psychiatric disorders – no. of patients (%)	1 (0.46)	2 (0.92)	1.00
Delirium	0 (0.00)	1 (0.46)	1.00
Depression	0 (0.00)	1 (0.46)	1.00
Manic episode	1 (0.46)	0 (0.00)	0.50
Accident	1 (0.46)	0 (0.00)	0.50
Traffic accident	1 (0.46)	0 (0.00)	0.50
Death of unknown cause – no. of patients (%)	0 (0.00)	3 (1.38)	0.25
Death of unknown cause	0 (0.00)	3 (1.38)	0.25

Safety Findings:

1. Adverse events reported by Denning et al: Only one patient had reported an adverse reaction related to itraconazole. A patient developed ankle edema which required diuretic therapy.

2. Adverse Events reported by Sharkey et al:
None of the eight patients experienced gastrointestinal symptoms attributable to itraconazole. No elevations in hepatic function values over baseline values were noted. Patient 8 after 6 weeks of itraconazole developed weakness, fatigue, orthostatic dizziness, intolerance of sun and heat, and edema prominent in the face and lower extremities. After 8 months of treatment with itraconazole at 600 mg/day, patient 1 was noted to have hypokalemia (potassium level, 2.5 meq/liter), hypertension, and mild edema. Supine and standing aldosterone concentrations in serum were mildly depressed (supine, <2.5 ng/dl [normal, 1 to 16 ng/dl]; standing, 3.2 ng/dl [normal, 4 to 31 ng/dl]) in this patient. Edema was also noted in four other patients.

For the entire group, there was a significant association of itraconazole treatment with reduced serum potassium levels. The authors report that hypokalemia could not be attributed to other concurrent medications. Although there was no significant difference between blood pressure values before and during treatment for the group, two patients (4 and 5) had significant elevations in blood pressure during treatment as compared with pretreatment.

One patient developed mild breast tenderness during treatment with 600 mg of itraconazole per day. The testosterone concentration in serum was 306 ng/dl (normal concentration, >280 ng/dl).

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3. Le et. al. reported adverse reactions in the itraconazole treatment group that are similar to the labeled AEs of itraconazole (i.e., GI adverse reactions, allergic reactions, metabolic/nutritional, and hematologic AEs). No cardiac adverse events associated with itraconazole were reported in these patients. However, it should be noted that these patients had HIV disease with severe systemic fungal infection and could have experienced these AEs secondary to their underlying disease.

Reviewer's Comment: The overall adverse reactions described in these literature publications are labeled AEs within the Itraconazole (Sporanox®) package insert. It is worth noting that in Patient #8 reported by Sharkey et al experienced signs and symptoms related to hypoadrenalism after initial itraconazole high dose at 600 mg for several months, then reduced to 400 mg as maintenance dose. The term hypoadrenalism per se is not mentioned in the Sporanox® label, however, adrenal insufficiency is mentioned under the Adverse Reactions section as reported in all clinical trials for systemic fungal diseases. Regarding TOLSURA's safety data in the PK studies, the GI symptoms, CNS, skin, and some abnormal laboratory results (i.e., liver enzymes, and hematologic tests) experienced by healthy subjects were also similar to the Sporanox® safety experience which are mentioned in its prescribing information.

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10 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Anti-Infective Drug Advisory Committee.

11 Pediatrics

The Applicant has based its reason for requesting a waiver for conducting pediatric studies on the point that the TOLSURA™ (itraconazole) 65 Capsules represent a drug product that does not contain a new active ingredient, new indication, new dosage form, new dosing regimen or a new route of administration. The pediatric population aged "birth to 16 years, including age groups often called neonates, infants, children, and adolescents" (21 CFR 201.57(f)(9)) are included in this waiver request for the proposed indications.

Reviewer's Comment: According to the clinical pharmacology TL, since the strength of SUBA Itraconazole proposed to be marketed is 65 mg, the frequency of the dosing regimen is the same, i.e., BID. However, the doses are not the same as Sporanox. This application did not go to PeRC since this product does not trigger PREA.

12 Labeling Recommendations

12.1. Prescribing Information

The complete review of TOLSURA 65 mg Capsules prescribing information has been conducted. This review included conversion of the prescribing information in to PLR/PLLR format and comparison of the labeling with the current labeling for the RLD.

The Division of Maternal and Pediatric Health (DPMH) was consulted for labeling review and recommendations related to the PLLR section of the TOLSURA™ label.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review and evaluate the proposed container labels and prescribing information for TOLSURA™ Capsules, 65 mg to identify areas of vulnerability that may lead to medication errors.

The Division of Drug Marketing, Advertising and Communication (DDMAC) was consulted to review the proposed container labels and prescribing information for TOLSURA™ Capsules, 65 mg and assess any misleading statements for the product eventual marketing.

Section	Proposed Labeling	Approved Labeling
Boxed Warning	(b) (4) CHF (b) (4)	CHF for all indications, DDI

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Section	Proposed Labeling	Approved Labeling
	(b) (4) DDI,	
Contraindications	(b) (4) Hypersensitivity	DDI, Contraindication with known hypersensitivity to itraconazole
Limitations of use	None	Not indicated for onychomycosis Not interchangeable or substitutable with other itraconazole products
Dosage and Administration	(b) (4)	Tabulated format and streamlined dosing instructions Specific population instruction were limited to Specific population section of the PI Recommendation for intake with food only
Warnings	(b) (4) DDI and Hepatotoxicity, Neuropathy, and Hearing Loss warnings	CHF, Hepatotoxicity, DDI, Cardiac Dysrhythmia, Neuropathy, Hearing Loss, Hypersensitivity
Adverse Reactions	(b) (4)	Removed (b) (4)
Specific Populations		Updated Pregnancy section with new published information, relocated nonclinical study findings to section 13
Pharmacokinetics		Updated with the recommendations from the Clinical Pharmacology Labeling guidance
Microbiology		Updated

12.2. Patient Labeling

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Patient Labeling for TOLSURA 65 mg capsules has been updated to be consistent with Full Prescribing Information.

13 Risk Evaluation and Mitigation Strategies (REMS)

No safety issues beyond those described in the RLD product labeling were identified during review to require REMS.

14 Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments.

15 Appendices

15.1. References

1. David Allen, Dustin Wilson, Richard Drew & John Perfect (2015) Azole antifungals: 35 years of invasive fungal infection management, Expert Review of Anti-infective Therapy, 13:6, 787-798, DOI: 10.1586/14787210.2015.1032939.

2. Le et al: A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis N Engl J Med. 2017 Jun 15;376(24):2329-2340. doi: 10.1056/NEJMoa1613306.

3. Patricia K. Sharkey, Michael G. Rinaldi, James F. Dunn, Thomas C. Hardin, Richard J. Fetchick, and John R. Graybill: High-Dose Itraconazole in the Treatment of Severe Mycoses Antimicrobial Agents and Chemotherapy, Apr. 1991, p. 707-713 Vol.

4. David W. Denning: Itraconazole Therapy for Cryptococcal Meningitis and Cryptococcosis Arch Intern Med Vol 149 October 1989, 2301-2308.

5. Sporanox® 100 mg capsules prescribing information -May 8, 2018

6. Centers For Disease Control and Prevention (CDC)-Fungal Diseases.

15.2. Financial Disclosure

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According to the Applicant, they certify that they have not entered into any financial arrangement with the listed clinical investigators. The applicant also certifies that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The applicant certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Covered Clinical Study (Name and/or Number): 11750701/MPG-016; 2013-3188/MPG-009; A15.0155/MPG-012; 2016-4155/MPG-013; 2017-4310/MPG-015; 2017-4313/MPG-017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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15.3. Nonclinical Pharmacology/Toxicology

No carcinogenicity data were submitted with this NDA.

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Individual Study Reviews

Study Number 2013-3188 (Protocol Number MPG009): The Relative Bioavailability of Single Oral doses of SUBA®-itraconazole 65 mg capsule (Mayne) compared to SPORANOX® 100 mg capsule (Janssen) administered under Fasted and Fed conditions in Healthy Adult Volunteers

Study Centre(s):
Clinical Facility:
(b) (4)
(b) (4)

Clinical Laboratory Facility:
(b) (4)
(b) (4)

Bioanalytical Facility:
(b) (4)
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)
(b) (4)

Objectives:
The objective of this study is to evaluate the relative bioavailability of SUBA®-itraconazole 65 mg capsules (Test)) compared to the currently marketed formulation of SPORANOX® (itraconazole) 100 mg capsules (Reference) when administered to healthy adult subjects as single oral doses under fasted and fed conditions.

Methodology:

- This is an open-label, single-dose, randomized, four-period, four-treatment, four-sequence, crossover, replicate designed study in healthy male and female subjects.

1. Concentrations of itraconazole were measured from samples collected over a 120-hour interval after dosing in each period.
2. The following PK data were calculated for itraconazole, the latter for informational purposes:
    - Plasma concentrations over time
    - Subject, period, sequence, treatment

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- AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, and $T_{1/2}$
- Inter-subject and intra-subject variability.

Test Product (Treatments A and B):
SUBA®-itraconazole 65 mg capsules (Mayne Pharma International Pty Ltd., Australia)
Batch No.: 961007
Potency: 98.3% of label claim
Expiry Date: August 2013
Dose: 65 mg
Mode of Administration: **Treatment A: fasted**; **Treatment B: fed**

Reference Product (Treatments C and D):
SPORANOX 100 mg capsule (Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., USA)
Lot No.: 2LG370
Potency: 101.4% of label claim
Expiry Date: 05-14
Dose: 100 mg
Mode of Administration: **Treatment C: fasted**; **Treatment D: fed**

Food Administration
In each period, an optional pre-study snack was provided to each subject after check-in and prior to fasting. For fasted periods, subjects fasted overnight for at least 10 hours prior to drug administration. For fed periods, subjects fasted for at least 10 hours prior to the start of a high fat, high calorie breakfast. Subjects were served a high fat, high calorie breakfast 30 minutes prior to drug administration. After dosing, all subjects fasted for at least 4 hours post-dose in all periods. The meal composition of the high fat, high calorie breakfast and nutritional information was consistent with the FDA recommended high-fat breakfast, as follows:

Breakfast Menu
Standardized Breakfast Menu
Two eggs (fried in butter)
Two strips of bacon (fried)
Two slices of white toast with 10 g butter (2 pats)
4 oz hash brown potatoes
8 oz full-fat milk
The meal contained approximately:
Protein calories 150
Carbohydrate calories 250
Fat calories 500

Bioanalytical Procedures

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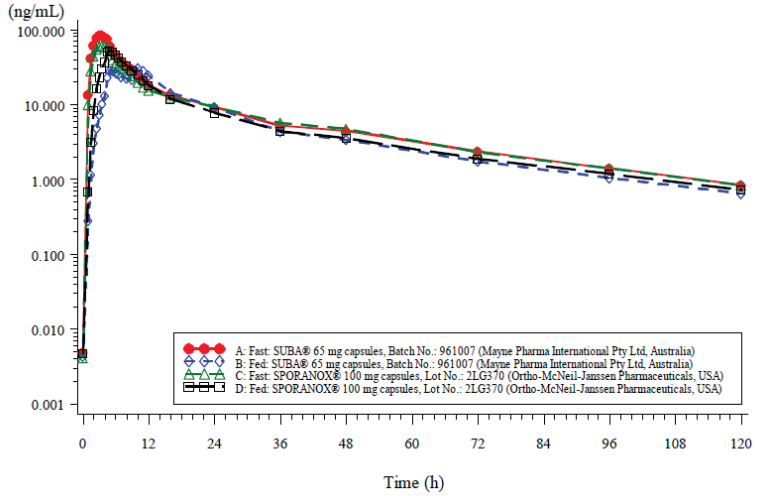
Subject plasma concentrations of itraconazole were measured using a reversed phase liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method (PMRI-1435-13 v.00) developed and validated at the Bioanalytical Laboratory (b) (4) The method involved liquid-liquid extraction. The standard calibration range was from 0.200 to 300 ng/mL for Itraconazole and from 0.500 to 400 ng/mL for using a plasma sample volume of 0.200 mL.

- *Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of <12% and accuracy of 92.5-99.5%. The inter-day precision and accuracy were also acceptable at 8.6% and 96.5%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.*

PHARMACOKINETIC RESULTS:
Mean plasma concentration-time profiles for itraconazole are as follows:

Figure 1: Mean Itraconazole Plasma Concentration-Time Semi Logarithmic Profiles; A: n = 51; B: n = 50; C: n = 52; D: n = 51



The summary results of PK and statistical analyses are as follows:

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Table 1. Itraconazole PK Results

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean (GCV%)	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
Cmax	**A**	51	111.910 (44)	101.612 (51)	**A vs C**	161.75	141.40 - 185.02	42
(ng/mL)	**B**	50	50.299 (50)	43.563 (75)	**B vs D**	80.26	67.61 - 95.27	55
	C	52	74.362 (57)	62.821 (63)	**B vs A**	42.87	36.61 - 50.20	50
	D	51	62.224 (55)	54.279 (61)	**D vs C**	86.40	74.38 - 100.37	48
					A vs D	187.20	164.23 - 213.40	41
AUCt	**A**	51	964.567 (45)	864.483 (55)	**A vs C**	123.35	110.68 - 137.47	34
(ng·h/mL)	**B**	50	633.713 (47)	564.352 (73)	**B vs D**	90.20	78.22 - 104.01	45
	C	52	838.298 (56)	700.820 (66)	**B vs A**	65.28	57.60 - 73.99	39
	D	51	713.922 (56)	625.683 (65)	**D vs C**	89.28	78.60 - 101.41	40
					A vs D	138.17	124.39 - 153.47	33
AUCinf	**A**	51	1006.534 (45)	901.266 (53)	**A vs C**	122.76	109.72 - 137.34	35
(ng·h/mL)	**B**	48	684.773 (46)	625.635 (51)	**B vs D**	94.67	85.35 - 105.01	32
	C	52	879.762 (57)	734.193 (64)	**B vs A**	69.42	63.76 - 75.58	26
	D	51	754.350 (58)	660.827 (61)	**D vs C**	90.01	79.34 - 102.11	40
					A vs D	136.38	122.81 - 151.46	33
Kel	**A**	51	0.0232 (23)					
(1/h)	**B**	48	0.0226 (23)					
	C	52	0.0242 (22)					
	D	51	0.0218 (25)					
Thalf	**A**	51	31.45 (23)					
(h)	**B**	48	32.48 (26)					
	C	52	29.95 (22)					
	D	51	34.02 (30)					
			Median	*Range*		*Hodges-Lehmann Estimate*	*Wilcoxon 90%Confidence Interval*	*Asymptotic 90% Confidence Interval?*
Tmax	**A**	51	2.50	1.50- 5.00	**A vs C**	0.000	-0.25 , 0.25	-0.25 , 0.25
(h)	**B**	50	7.50	4.50-24.00	**B vs D**	3.000	2.25 , 3.75	2.25 , 3.75
	C	52	3.00	1.50- 4.52	**B vs A**	5.000	4.25 , 5.75	4.25 , 5.75
	D	51	5.00	2.50-11.00	**D vs C**	2.250	1.75 , 2.50	1.75 , 2.50
					A vs D	-2.250	-2.50 , -2.00	-2.50 , -2.00

Geometric means are based on the least-squares means estimated by Proc Mixed
GCV% = CV% of the geometric means based on the standard error of the least-squares means estimated by Proc Mixed

Treatment A (Test1)	*Fast: SUBA® 65 mg capsules, Batch No.: 961007 (Mayne Pharma International Pty Ltd, Australia)*
Treatment B (Test2)	*Fed: SUBA® 65 mg capsules, Batch No.: 961007 (Mayne Pharma International Pty Ltd, Australia)*
Treatment C (Ref1)	*Fast: SPORANOX® 100 mg capsules, Lot No.: 2LG370 (Ortho-McNeil-Janssen Pharmaceuticals, USA)*
Treatment D (Ref2)	*Fed: SPORANOX® 100 mg capsules, Lot No.: 2LG370 (Ortho-McNeil-Janssen Pharmaceuticals, USA)*

The analysis of the residuals identified the AUCt and Cmax values obtained for Subject (b) (6) Treatment B as outliers. The exclusion of these data led to the following summary statistics:

Table 2. Itraconazole PK Results (Data for Subject 18 Treatment B Excluded)

Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean (GCV%)	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
Cmax	**A**	51	111.910 (44)	101.618 (52)	**A vs C**	161.76	141.17 - 185.34	43
(ng/mL)	**B**	49	51.276 (48)	46.265 (55)	**B vs D**	85.18	74.09 - 97.92	44
	C	52	74.362 (57)	62.821 (62)	**B vs A**	45.53	40.17 - 51.60	39
	D	51	62.224 (55)	54.316 (60)	**D vs C**	86.46	74.52 - 100.31	48
					A vs D	187.09	164.02 - 213.40	41
AUCt	**A**	51	964.567 (45)	864.413 (53)	**A vs C**	123.34	110.11 - 138.17	35
(ng·h/mL)	**B**	49	646.200 (44)	597.502 (50)	**B vs D**	95.45	85.99 - 105.95	32
	C	52	838.298 (56)	700.820 (64)	**B vs A**	69.12	63.49 - 75.26	26
	D	51	713.922 (56)	625.956 (61)	**D vs C**	89.32	78.60 - 101.50	40
					A vs D	138.09	124.09 - 153.68	33
AUCinf	**A**	51	1006.534 (45)	901.266 (53)	**A vs C**	122.76	109.72 - 137.34	35
(ng·h/mL)	**B**	48	684.773 (46)	625.635 (51)	**B vs D**	94.67	85.35 - 105.01	32
	C	52	879.762 (57)	734.193 (64)	**B vs A**	69.42	63.76 - 75.58	26
	D	51	754.350 (58)	660.827 (61)	**D vs C**	90.01	79.34 - 102.11	40
					A vs D	136.38	122.81 - 151.46	33

SPONSOR'S CONCLUSIONS:

The intra-subject-within-reference standard deviations (C versus D) were larger than

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0.294 for all three parameters: 0.388, 0.385 and 0.463 for itraconazole AUCt, AUCinf and Cmax, respectively. Therefore, wider bioequivalence acceptance ranges were calculated for AUCt (70.72-141.41%), AUCinf (70.94-140.97%) and Cmax (66.14-151.20%).

Fasting Conditions (A vs. C): The test drug product (SUBA® 65 mg capsules) exhibited 23% larger AUCt and AUCinf and 62% larger Cmax when compared to the reference drug product (SPORANOX® 100 mg capsules) under fasting conditions. The test/reference geometric mean ratios (T/R) were 123.35%, 122.76% and 161.75% for AUCt, AUCinf and Cmax respectively. The 90% confidence intervals for AUCt (110.68-137.47%) and for AUCinf (109.72-137.34%) were within the wider bioequivalence acceptance ranges estimated for these parameters. The upper limit of the 90% confidence interval for Cmax (141.40-185.02%) was outside of the wider bioequivalence range (66.14-151.20%).

There is no significant difference between the two formulations with respect to the Tmax parameter. The median difference is zero (0.00) and the Wilcoxon 90% confidence interval is -0.25 to +0.25 hours. Therefore, SUBA® 65 mg capsules exhibited bioequivalent extent of exposure (based on AUCt and AUCinf comparisons) but not bioequivalent peak exposure (based on Cmax comparison) to the reference SPORANOX® 100 mg capsules when administered as a single dose under fasting conditions.

Fed Conditions (B vs. D): The test drug product (SUBA® 65 mg capsules) exhibited 10% lower AUCt, 5% lower AUCinf and 20% lower Cmax when compared to the reference drug product (SPORANOX® 100 mg capsules) under fed conditions. The T/R ratios were 90.20%, 94.67% and 80.26% for AUCt, AUCinf and Cmax respectively. The 90% confidence intervals for AUCt (78.22-104.01%), for AUCinf (85.35-105.01%) and Cmax (67.61-95.27%) are all within the wider bioequivalence acceptance ranges estimated for each of these parameters. The median Tmax estimated for the test formulation is significantly larger than the reference. The median difference is 3.00 hours with a Wilcoxon 90% confidence interval of 2.25 to 3.75 hours.

Therefore, SUBA® 65 mg capsules exhibited bioequivalent extent of exposure (based on AUCt and AUCinf comparisons) and bioequivalent peak exposure (based on Cmax comparison) to the reference SPORANOX® 100 mg capsules when administered as a single dose under fed conditions.

Food effect:
Test Formulation (B vs. A): The presence of food decreases the bioavailability of the test formulation. The mean AUCt and AUCinf are 35% and 31% lower and the mean Cmax is 57% lower when the test formulation is administered after a high-fat, high- calorie breakfast. The T/R ratios were 65.28%, 69.42% and 42.87% for AUCt, AUCinf and Cmax respectively. Due to the low values for the geometric mean ratios, the corresponding 90% confidence intervals for AUCt (57.60 - 73.99%), AUCinf (63.76 - 75.58%) and Cmax (36.61 - 50.20%), were not within the 80-125%. The test drug product, SUBA® 65 mg capsules, exhibited a significant food effect.

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Reference Formulation (D vs. C): The reference formulation also exhibited lower bioavailability in the presence of food: the mean AUCt, AUCinf and Cmax were 11%, 10 and 14% lower respectively. The T/R ratios were 89.28%, 90.01% and 86.40% for AUCt, AUCinf and Cmax respectively. The corresponding 90% confidence intervals: 78.60-101.41%, 79.34-102.11% and 74.38-100.37% were not within the 80-125% range.

Overall the presence of food appears to influence to a larger extent the bioavailability of the test formulation than that of the reference. The exclusion of treatment B data for Subject (b) (6) increased the ratio of the geometric means for the contrast that involved treatment B and reduced the inter-subject variances for this treatment. It generated very small changes in the final statistics for the other treatment comparisons. It did not affect the results for the AUCinf since this parameter was not estimated for Subject (b) (6) treatment B.

The overall conclusions on comparative bioavailability or the effect of food were not changed by this exclusion.

Reviewer's Conclusions/Comments:

1. The wider confidence limits proposed in the sponsor's report are not accepted by the FDA. The standard BE criteria of 80-125% for AUC and Cmax will be applied for this study,
2. Clearly, under fasting conditions the 65 mg SUBA capsules are not BE to 100 mg SPORANOX capsules and the exposure of itraconazole following administration of the SUBA product is 23% higher (AUCinf), 62% higher (Cmax) compared to the SPORANOX capsule.
3. Under fed conditions the 65 mg SUBA capsules are not strictly BE to 100 mg SPORANOX capsules. The exposure of itraconazole following administration of the SUBA product is 5% lower (AUCinf) and 20% lower (Cmax) compared to the SPORANOX capsule. The 90% confidence intervals for AUCinf (85.35-105.01%) and Cmax (67.61-95.27%) indicate that BE criteria was met for the AUCinf but not for Cmax.
4. The systemic exposure of itraconazole was lower after administration of SUBA capsules compared to the SPORANOX capsules. Food decreased the bioavailability of the SUBA formulation. The mean AUCinf is 31% lower and the mean Cmax is 57% lower when the SUBA formulation is administered after a high-fat, high calorie breakfast.
5. Interestingly, the rate (Cmax) and extent (AUC) of exposure to itraconazole following administration of SPORANOX capsules were lower under fed conditions vs. fasted conditions. It is noteworthy that the approved labeling for SPORANOX capsules indicates that the oral BA of itraconazole is higher under fed conditions and the labeling recommends giving SPORANOX with food. The reason for this inconsistent result with SPORANOX was not addressed by the Sponsor and remains unknown.

Study Number A15.0155 (Protocol Number MPG012): An open label, randomized, two-treatment, two-sequence, two period, cross-over, multiple-dose, steady-state, oral

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bioequivalence study of SUBA®-Itraconazole Capsules 65 mg [2 X 65 mg] (Test) and SPORANOX® (Itraconazole) Capsules 100 mg [2 X 100 mg] (Reference) in healthy, adult, human subjects under fed conditions.

Study Centre(s):
Clinical Facility:
(b) (4)

Clinical Laboratory Facility:
(b) (4)

Bioanalytical Facility:
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)

Objectives:
Objective:
Primary Objective:
To compare the rate and extent of absorption SUBA-Itraconazole Capsules 65 mg [2 X 65 mg] (Test) of Mayne Pharma International Pty Ltd., with SPORANOX (Itraconazole) Capsules 100 mg [2 X 100 mg] (Reference) of Janssen Pharmaceuticals, Inc.
Secondary Objective:
To monitor the adverse events and to ensure the safety of the subjects.

Methodology:
An open label, randomized, two-treatment, two-sequence, two-period, cross-over, multiple-dose, steady-state, oral bioequivalence study in healthy, adult, human subjects under fed conditions. 20 subjects ranging in age from 19 - 67 years with a body mass index (BMI) of 19.72 – 31.83 kg/m^2 were enrolled.

Drug product doses:
The following doses of drug product were administered under fed conditions:

- Test: SUBA-Itraconazole Capsules 2 x 65 mg (130 mg) QD x 15 days
- Reference: Sporanox (Itraconazole) Capsules 2 x 100 mg (200 mg) QD x 15 days

Dietary Plan: Day 1 to 14:

Reference ID: 4360457

Subjects were provided breakfast prior to administration of drug product in each period.
Day 15:
Following an overnight fast of at least 10 hours, subjects were provided high-fat high- calorie breakfast of approx. 1000 Cal. (approx. 60% of total calories coming from fat) 30 minutes prior to administration of the drug product. Study subjects consumed this meal in 30 minutes or less and drug product was administered 30 minutes after start of the meal. No food was allowed for at least 4 hours after dose of study drug (day 15). A washout period of 20 days was maintained from after the dose on Day 15 in Period I to the dose in Period II (Day 1).

Food Administration
High-fat high-calorie breakfast consisted of the following:
Two (2) eggs fried in butter
Two (2) strips of bacon
Two (2) slices of toast with butter
Four (4) ounces of hash brown potatoes
Eight (8) ounces of whole milk
Post dose meals on Day 15 were provided approximately at 4.5, 10 and 13 hours respectively during each period.

Bioanalytical Procedures
The plasma samples of subjects were analyzed using a validated LC-MS/MS method for itraconazole at the bioanalytical laboratory (b) (4) The analysis was conducted as per the applicable Method No: AP 020_01 for itraconazole. Calibration curve of 6.000 ng/mL to 2,000 ng/mL for itraconazole were used to determine the concentrations of itraconazole in the samples of various subjects.

Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of 0.8%-4.6% and accuracy of 92.5-99.5%. The inter-day precision and accuracy were also acceptable at 8.6% and 96.5%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.

PHARMACOKINETIC RESULTS:
The PK parameters listed below were derived individually for each analyzed subject from the concentration vs. time data of itraconazole in plasma. Calculation of pharmacokinetic parameters was done for itraconazole by non-compartmental methods.

The mean pharmacokinetic parameters and statistical analyses of itraconazole for SUBA Itraconazole and SPORANOX are summarized below.

Reference ID: 4360457

Descriptive PK Statistics for Itraconazole (N= 20)

Parameter (Unit)	Mean ± SD (Un-transformed data)	
	Reference Product (R)	Test Product (T)
$C_{max\ ss}$ (ng/mL)	518.3585 ± 201.50537	596.9700 ± 175.85593
$C_{min\ ss}$ (hr.ng/mL)	231.7000 ± 94.04970	240.7885 ± 101.75947
$AUC_{0-\tau}$ (hr. ng/mL)	7668.7117 ± 2926.79260	8308.4988 ± 2866.27224
$T_{max\ ss*}$ (hr)	5.00 (2.50-7.00)	5.50 (4.50-11.02)
$C_{avg\ ss}$	319.5296 ± 121.94970	346.1874 ± 119.42791
Fluctuation (%)	100.4067 ± 52.59579	114.7547 ± 61.26907
Swing (%)	127.5366± 47.68595	194.8124 ± 181.94210

**For $T_{max\ ss}$ Median has been represented instead of Mean and Range instead of SD.*

Parameter (Unit)	(Ln-transformed) Geometric Least Square Mean			90% Confidence Interval T vs R	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)	Ratio (T/R)%			
$C_{max\ ss}$	566.2488	463.2271	122.24%	99.86-149.64	38.0	57
$C_{min\ ss}$	213.1565	214.4965	99.38%	87.90-112.35	22.5	91
$AUC_{0-\tau}$	7723.2489	6717.5234	114.97%	94.62-139.70	36.5	60

SPONSOR'S CONCLUSIONS:

Cmax ss:

The ratio of geometric least square mean of Test Product and Reference product for Ln-transformed pharmacokinetic parameter, Cmax ss was 122.24%. The 90% confidence interval for the ratio of geometric least squares mean was found to be 99.86-149.64%. This interval is not within the acceptance limits of 80.00-125.00%.

Cmin ss:

The ratio of geometric least square mean of Test Product and Reference product for Ln-transformed pharmacokinetic parameter, Cmin ss was 99.38%. The 90% confidence interval for the ratio of geometric least squares mean was found to be 87.90-112.35%. This interval is within the acceptance limits of 80.00-125.00%.

Extent of Absorption AUC0-τ:

The ratio of geometric least squares mean test product and reference product for Ln-transformed pharmacokinetic parameter, AUC0-τ was 114.97%. The 90% confidence interval for the ratio of geometric least square mean was found to be 94.62-139.70%. This interval is not within the acceptance limits of 80.00-125.00%. Based on these results, SUBA-Itraconazole Capsules 65 mg [2 X 65 mg] was not bioequivalent with that of SPORANOX capsules 100 mg in healthy, adult, human subjects under fed conditions.

Reviewer's Conclusions/Comments:

Reference ID: 4360457

1. The reviewer confirmed the BE analysis with Phoenix software using the Cmax and AUC dataset provided by the Sponsor. The geometric mean ratios and CIs reported by the Sponsor are confirmed and acceptable.
2. Based on the results of this study, the main conclusion that can be reached is that at a dose of 130 mg SUBA capsules (2 × 65 mg) given under fed conditions, neither the steady-state rate (Cmax) nor extent (AUC) of itraconazole absorption are BE to SPORANOX capsules in the healthy subjects in this study.
3. Although the Cmin ss results met the BE criteria for SUBA capsules, these results are not useful in the context of interpreting the BE results from this study.

Study Number 2016-4155 (Protocol Number MPG013): An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period, Crossover, Multiple-Dose, Oral Bioequivalence Study of Lozanoc® (Itraconazole) Capsules 65 mg [2 X 65 mg] (Test) and Sporanox® (Itraconazole) Capsules 100 mg [2 X 100 mg] (Reference) Administered Three Times Daily (8 Hours apart) from Days 1-3 and Once a Day (2 X 65 mg of Test/2 X 100 mg of Reference) on Day 4 in Healthy, Adult, Human Subjects, under Fed Conditions

Study Centre(s):
Clinical Facility:
(b) (4)

Clinical Laboratory Facility:
(b) (4)

Bioanalytical Facility:
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)

Objectives and Dose Administration:
The primary objective of this study was to compare the steady-state rate and extent of absorption of:

Reference ID: 4360457

- **TEST:** SUBA-itraconazole Capsules dosed at 130 mg (2 x 65 mg) TID (total daily dose 390 mg) on Days 1 to 3, and 130 mg on Day 4
- **REFERENCE:** Sporanox® (itraconazole) Capsules dosed at 200 mg (2 x 100 mg) TID (total daily dose 600 mg) on Days 1 to 3, and 200 mg on Day 4

The secondary objective of this study was to evaluate safety and tolerability of SUBA as compared to Sporanox.

Methodology:
This was an open-label, multiple-dose, randomized, two-period, two-treatment, two sequence, crossover study. Subjects were administered two capsules of the test or reference product three times daily on Days 1-3 after completion of a standardized meal, and once on the morning of Day 4 after completion of a high-fat, high-calorie breakfast. Concentrations of itraconazole were measured in plasma from pre-dose samples collected on the mornings of Days 1, 2, and 3, and over an 8-hour interval after dosing on Day 4 in both periods.

The two study periods were separated by a washout of 21 days, corresponding to more than five times the expected half-life of itraconazole to prevent any possible carryover effect.

Number of Subjects:
- Planned for inclusion and enrolled in the study: 16 subjects
- Completed the study: 15 subjects
    - One (1) subject was dismissed from the study at Period 2 check-in for non-compliance with study restrictions.
- Included in the safety dataset: 16 subjects
- Included in the PK and statistical datasets: 15 subjects
    - The subject who did not complete the study did not accrue sufficient data to allow for the calculation of Cmax,ss, Ctrough, and AUCtau parameters in both periods, and thus was not included in the PK and statistical analyses.

Test Product:
SUBA®-itraconazole 65 mg capsules (Mayne Pharma International Pty Ltd., Australia)
Batch No.: 263862

Reference Product:
SPORANOX 100 mg capsule (Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., USA)
Lot No.: 16BG227

Food Administration
For fasted periods, subjects fasted overnight for at least 10 hours prior to drug administration. For fed periods, subjects fasted for at least 10 hours prior to the start of a high fat, high calorie breakfast. After dosing, all subjects fasted for at least 4 hours post-dose in all periods. Subjects

Reference ID: 4360457

were served a high fat, high calorie breakfast 30 minutes prior to drug administration. The meal composition and nutritional information was as follows

Breakfast Menu
Standardized Breakfast Menu
Two eggs (fried in butter)
Two strips of bacon
Two slices of white toast with 10 g butter (2 pats)
4 oz hash brown potatoes
8 oz full-fat milk
The meal contained approximately:
Protein calories 133
Carbohydrate calories 260
Fat calories 526

Bioanalytical Procedures
Subject plasma concentrations of itraconazole were measured per a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method (PMRI-1665-16) developed and validated at the Bioanalytical Laboratory [redacted] (b) (4) The standard calibration range was from 25-2000 ng/mL for itraconazole using a plasma sample volume of 0.200 mL.

Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of <10% and accuracy of: 83.6% to 96.0%. *The inter-day precision and accuracy were also acceptable at <10% and 89%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.*

PHARMACOKINETIC RESULTS:
The results of the PK and statistical analyses for itraconazole are presented in Table 1.

Table 1. Summary of PK Study Results for Itraconazole

Based on Pharmacokinetic and Statistical Dataset								
Parameter	**Trt**	**n**	**Arithmetic Mean (CV%)**	**Geometric Mean**	**Contrast**	**Ratio (%)**	**90% Confidence Interval**	**Intra-Sbj CV(%)**
C_{max_ss}	**A**	15	1085.0 (26)	1055.3	**A vs B**	114.54	103.40 - 126.88	16
(ng/mL)	**B**	15	944.9 (27)	921.3				
C_{trough}	**A**	15	918.9 (32)	881.1	**A vs B**	107.37	95.58 - 120.62	18
(ng/mL)	**B**	15	844.3 (30)	820.6				
AUC_{tau}	**A**	15	7150.8 (30)	6881.7	**A vs B**	110.35	100.10 - 121.66	15
(hr*ng/mL)	**B**	15	6390.0 (26)	6236.2				

Reference ID: 4360457

SPONSOR'S CONCLUSIONS:

The total and peak exposure of itraconazole, as measured by AUCtau and Cmax,ss, respectively, was approximately 10% and 15% higher following Treatment A than for Treatment B (ratios of AUCtau=110.35% and Cmax,ss=114.54%). Itraconazole concentrations at the end of the dosing interval were approximately 7% higher for Treatment A compared to Treatment B.

Reviewer's Comments:

1. The sponsor's conclusions are acceptable. The results of this study indicate that the steady-state rate and extent of absorption of itraconazole following oral doses of 390 mg/day x 3 days, followed by 130 mg on Day 4 of SUBA-Itraconazole are comparable to that of SPORANOX following oral doses of 600 mg/day x 3 days, followed by 200 mg on Day 4, in healthy, adult, human subjects under fed conditions

Reference ID: 4360457

Study Number 2017-4310 (Protocol Number MPG015: An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period, Cross-over, Multiple-Dose, Steady-State, Oral Bioequivalence Study of SUBA®-Itraconazole Capsules 65 mg [2 x 65 mg BID] (Test) and SPORANOX® (Itraconazole) Capsules 100 mg [2 x 100 mg BID] (Reference) in Healthy, Adult, Human Subjects under Fed Conditions

Study Centre(s):
Clinical Facility:
(b) (4)

Clinical Laboratory Facility:
(b) (4)

Bioanalytical Facility:
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)

Objectives:
The objective of this study was to evaluate the bioequivalence between SUBA-itraconazole 65 mg Capsules and SPORANOX® (itraconazole) 100 mg after twice daily administration (12 hours apart) of two capsules (2×65 mg capsules) per administration on Days 1-14 and one administration of two capsules (2×65 mg capsules) on Day 15, in healthy, adult, human subjects under fed conditions. The secondary objective was to monitor the adverse events (AEs) and to ensure the safety of the subjects.

Methodology:
This was an open-label, multiple-dose, randomized, two-period, two-treatment, two sequence, crossover, bioequivalence study.

Treatments Administered
In each period, subjects received one of the following two treatments

Reference ID: 4360457

Treatment A SUBA-Itraconazole 65 mg Capsules (Test Product)
Days 1-14 130 mg BID [total dose = 260 mg per day]

- First dose at 0-hour – 130 mg (2 x 65 mg) administered 30 minutes after the start of a standardized breakfast;
- Second dose at 12-hour – 130 mg (2 x 65 mg) administered 30 minutes after the start of a standardized meal.

Day 15 130 mg x 1

- 130 mg (2 x 65 mg) administered 30 minutes after the start of a high-fat, high calorie breakfast

Treatment B SPORANOX 100 mg Capsules (Reference Product)
Days 1-14 200 mg BID [total dose = 400 mg per day]

- First dose at 0-hour – 200 mg (2 x 100 mg) administered 30 minutes after the start of a standardized breakfast;
- Second dose at 12-hour – 200 mg (2 x 100 mg) administered 30 minutes after the start of a standardized meal.

Day 15 200 mg x 1

- 200 mg (2 x 100 mg) administered 30 minutes after the start of a high-fat, high calorie breakfast

Food Administration
After an overnight fast of at least 7.5 hours, subjects consumed a high-fat, high-calorie breakfast starting 30 minutes prior to drug administration. Contents of the breakfast are presented below:

	Calories (kcal)	Total Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs	140	10	0	12
14 g butter for cooking eggs	100	11	0	0
2 slices of toast	130	1	25	5
14 g of butter for toast	100	11	0	0
114 g of hash brown potatoes	200	10	24	2
236 mL of whole milk	150	8	11	8
2 slices of bacon	70	6	0	4
Total weight		57	60	31
Total calories (kcal)	890	513	240	124
Relative caloric content		58%	27%	14%

Bioanalytical Procedures
Subject plasma concentrations of Itraconazole were measured according to a liquid chromatographic (LC) tandem MS spectrometric detection (MS/MS) achiral method (PMRI-1712-17v.00) developed and validated at the Bioanalytical Laboratory (b) (4)

Reference ID: 4360457

(b) (4) The standard calibration range was from 1-600 ng/mL for Itraconazole using a plasma sample volume of 0.100 mL.

Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of <10% and accuracy of 96-110%%. The inter-day precision and accuracy were also acceptable at <10% and 103%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.

PHARMACOKINETIC RESULTS:
The results of the PK and statistical analyses for itraconazole are presented in Table 1.

Table 1. PK Results and Statistical Analysis of Itraconazole for Treatments A and B

Based on Statistical Dataset								
Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
C_{max_ss}	A	16	1667.5 (22)	1632.2	A vs B	111.99	104.87 - 119.59	11
(ng/mL)	B	16	1505.1 (27)	1457.5				
C_{trough}	A	16	1229.8 (29)	1187.4	A vs B	118.16	110.20 - 126.69	11
(ng/mL)	B	16	1034.4 (25)	1004.9				
AUC_{tau}	A	16	15943.6 (23)	15562.1	A vs B	110.64	104.01 - 117.70	10
(hr*ng/mL)	B	16	14529.5 (26)	14065.1				

Treatment A (Test) SUBA-itraconazole 65 mg Capsules (2 capsules on Days 1-14 BID, Day 15 QD),
Treatment B (Reference) Sporanox® (itraconazole) 100 mg Capsules (2 Capsules on Days 1-14BID, Day 15 QD).

SPONSOR'S CONCLUSIONS:
The total and peak itraconazole exposure was relatively similar between treatments (test/reference ratios of 110.64% for AUCtau and 111.99% for Cmax,ss). Itraconazole concentrations at the end of the dosing interval were approximately 18% higher for Treatment A compared to Treatment B. The 90% CIs of the relative mean plasma itraconazole Cmax,ss and AUCtau of the test to reference products were between 80.00 and 125.00%.

Overall, the test product, SUBA-itraconazole 65 mg Capsules (Mayne Pharma International Pty Ltd, Australia), exhibited equivalent total and peak exposure compared to the reference product, Sporanox® (itraconazole) 100 mg Capsules (Janssen Pharmaceuticals, Inc., USA), after twice daily administration of two capsules on Days 1-14 and one administration of two capsules on Day 15, in healthy, adult, human subjects under fed conditions.

Reference ID: 4360457

The administration of the study drugs was generally well-tolerated by the healthy subjects participating in this study. All TEAEs were mild in severity and resolved prior to the end of the study. No SAEs were reported in the conduct of this study and none of the TEAEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Reviewer's Comments:

- The results of this study indicate that the SUBA-itraconazole 65 mg Capsules, exhibited similar total and peak exposure compared to SPORANOX® 100 mg Capsules, after twice daily administration of 130 mg (2 x 65 mg) on Days 1-14 and one administration of 130 mg on Day 15, in healthy, adult, human subjects under fed conditions

Reference ID: 4360457

Study Number 11750701 (Protocol Number MPG016): A Comparative Bioavailability Study Comparing SUBA®-itraconazole Capsules (Mayne Pharma, Inc.) Co-Administered with Omeprazole Delayed-Release Capsules (Sandoz Inc.) in Healthy Adult Subjects

Study Centre(s):
Clinical Facility:
(b) (4)

Clinical Laboratory Facility:
(b) (4)

Bioanalytical Facility:
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)

Objectives:
Primary Objective: To evaluate the effect of multiple daily oral doses (steady-state conditions) of omeprazole delayed-release capsules (Sandoz, Inc.) on the pharmacokinetics of SUBA®-itraconazole capsules (Mayne Pharma International Pty Ltd.) after a single oral dose in healthy, adult male and female subjects under fasted conditions.

Methodology:
This was an open-label, two-period, two-treatment, fixed-sequence comparative bioavailability study under fasted conditions comparing the pharmacokinetics of a single oral dose of SUBA®-itraconazole capsules with and without co-administration of multiple daily doses of omeprazole delayed-release capsules under steady-state conditions. In Period I, subjects received a single 130 mg dose of Treatment A (2 x 65 mg SUBA®-itraconazole capsules) following an overnight fast of at least 10 hours. Subjects were confined at the clinical facility from at least 10 hours before dosing in Period I until after the 24-hour blood sample collection and returned to the clinical facility for the 36-, 48-, 60-, 72-, and 96-hour blood sample collections.

Reference ID: 4360457

In Period II, subjects received a single 40 mg dose of Treatment B (1 x 40 mg omeprazole delayed-release capsule) on study Days -6 through -1 in the clinical facility following an overnight fast of at least 4 hours (total cumulative dose of 240 mg of omeprazole over a 6-day period); breakfast was served in the clinical facility at 30 minutes following dosing. On study Day 1 subjects received a single 130 mg dose of Treatment A (2 x 65 mg SUBA®-itraconazole capsules) co-administered with the last of seven daily 40 mg doses of Treatment B (1 x 40 mg omeprazole delayed- release capsule) following an overnight fast of at least 10 hours. Subjects were dosed with Treatment B on study Days -6 through Day -2 in the clinical facility on an outpatient basis; the subjects arrived at the clinical facility at least 1 hour before dosing and remained at the clinical facility until at least 2 hours after dosing. Subjects were confined at the clinical facility from at least one hour before the time of the Day-1 Treatment B dosing until after the 24-hour blood sample collection (Day 2) and returned to the clinical facility for the 36-, 48-, 60-, 72-, and 96-hour blood sample collections (relative to dosing on Day 1). There was a 4-day washout interval between Treatment A dosing on Day 1 in each study period.

TREATMENT A:
SUBA®-Itraconazole 65 mg Capsule Mayne Pharma International Pty Ltd. Batch No.: 263862
Manufacture Date: September 2016

TREATMENT B:
Omeprazole Delayed-Release Capsules, USP 40 mg
Manufactured by Lek Pharmaceuticals d.d. for Sandoz Inc.
Lot No.: GX2030

Bioanalytical Procedures
Subject plasma concentrations of itraconazole were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method (PMRI-1712-17v.00) developed and validated at the Bioanalytical Laboratory (b) (4) The standard calibration range was from 1-600 ng/mL for itraconazole using a plasma sample volume of 0.100 mL. The plasma concentrations of omeprazole were not measured in this study.

Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of <10% and accuracy of 96-110%%. The inter-day precision and accuracy were also acceptable at <10% and 107%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.

PHARMACOKINETIC RESULTS:
Geometric means, ratio of means, and their associated 90% confidence intervals and intra-subject CV (ISCV%) values based on ANOVA (ln-transformed) are provided in Table 1 for itraconazole

Reference ID: 4360457

Table 1. Summary of Primary PK Parameters for Itraconazole

Parameter	Trt	LS Geometric Mean	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV(%)	P-value Treatment	90% CI Within No-Effect Boundary*
AUC $_{0-t}$ (h·ng/mL)	A	2640	A+B vs A (n=28)	121.66	107.82 to 137.28	27.0	0.0101	No
	A+B	3212						
AUC $_{0-\infty}$ (h·ng/mL)	A	2846	A+B vs A (n=28)	122.19	108.72 to 137.32	26.1	0.0069	No
	A+B	3478						
C_{max} (ng/mL)	A	213.0	A+B vs A (n=28)	130.90	111.42 to 153.79	36.5	0.0083	No
	A+B	278.8						

Treatment A = SUBA-Itraconazole 130 mg (2 x 65 mg) alone x 1 dose
Treatment B = Omeprazole 40 mg QD x 7 days + SUBA-Itraconazole 130 mg x 1 dose on Day 7]

SPONSOR'S CONCLUSIONS:
There was a 22% increase in AUC of itraconazole in the presence of omeprazole and a 30% increase in Cmax. The metabolite GMRs for AUC and Cmax (124-129%) are concordant with those of itraconazole. Therefore, a lack of effect of omeprazole on the pharmacokinetics of itraconazole cannot be concluded based on data from the 28 subjects who completed this study.

Co-administration of SUBA®-itraconazole capsules with omeprazole is not expected to affect its efficacy given that itraconazole bioavailability is increased and not reduced in the presence of omeprazole. Also, co-administration of SUBA®-itraconazole capsules with omeprazole is not expected to affect its safety given that the increase in total and peak plasma exposures are 22-31% and the two treatments were generally well tolerated by the healthy adult subjects during the study. There were no serious adverse events reported during the study. Therefore, SUBA®-itraconazole capsules can be taken concurrently with omeprazole-containing products.

Reviewer's Conclusions/Comments:

- This study was conducted under fasting conditions and SUBA-Itraconazole was given as a single dose of 130 mg.
- The sponsor's conclusions are not acceptable.
- The study results indicate that there is an increase in the systemic exposure of itraconazole, in terms of both rate (Cmax mean increase ~31%) and extent (AUCinf) mean increase ~22%) of absorption following co-administration of a single dose of 130 mg SUBA-Itraconazole with 40 mg omeprazole dosed to steady-state.
- The 90% CI's for Cmax and AUC(0-inf) are both outside the 80% to 125% no effect boundary, indicating there is a significant drug-drug interaction between omeprazole and SUBA-Itraconazole.

Reference ID: 4360457

- Furthermore, the magnitude of the upper bounds of the 90% CI's indicated that the increases in Cmax and AUC(0-inf) can be as high as 54% and 37%, respectively, if omeprazole is co-administered with SUBA-Itraconazole.
- Of particular concern, in terms of safety, is the increase in the Cmax of itraconazole. It is noteworthy that the magnitude of the increase in itraconazole Cmax (noted in the bullets above) with co-administration of SUBA-Itraconazole and omeprazole is with a single dose of SUBA, and does not take into account the known non-linear PK and potential plasma accumulation of itraconazole following dosing of SUBA to steady-state.
- Thus, the reviewer does not agree with the Sponsor's conclusions that SUBA-Itraconazole capsules can be taken concurrently with omeprazole containing products, but rather, the results from this study indicate that caution should be exercised when SUBA-Itraconazole capsules are co-administered with TOLSURA.

Reference ID: 4360457

Study Number 2017-4313 (Protocol Number MPG017): An Open-Label, Randomized, Two-Treatment, Two-Sequence, Two-Period, Cross-over, Multiple-Dose, Steady-State, Food Effect Study of SUBA-Itraconazole Capsules 65 mg [2 X 65 mg BID] Test in Healthy, Adult, Human Subjects under Fasting and Fed Conditions

Study Centre(s):
Clinical Facility:
(b) (4)

Clinical Laboratory Facility:
(b) (4)

Bioanalytical Facility:
(b) (4)

Pharmacokinetic and Statistical Facility:
(b) (4)

Objectives:
The primary objective of this study was to evaluate the effect of food on SUBA-itraconazole 65 mg Capsules (Mayne Pharma International Pty Ltd, Australia) after twice daily administration (12 hours apart) of 130 mg (2 x 65 mg) on Days 1-14 and one administration of 130 mg on Day 15, in healthy, adult, human subjects.

The secondary objective of this study was to monitor the adverse events and to ensure the safety of the subjects.

Methodology:
This was an open-label, multiple-dose, randomized, two-period, two-treatment, two sequence, crossover, comparative fed-fasted bioavailability study.

Study Population
24 healthy adult, non-smoking, male and female volunteers, aged 18 to 55 years were enrolled in the study.

Reference ID: 4360457

Treatments

Treatment A 130 mg SUBA-Itraconazole Fed

- Days 1-14: [total dose = 260 mg per day]
    - First dose at 0-hour – 130 mg 30 minutes after the start of a standardized breakfast;
    - Second dose at 12-hour – 130 mg administered 30 minutes after the start of a standardized dinner.

Notes:

- Subjects fasted for at least 10 hours prior to the consumption of the standardized breakfast, and at least 4 hours after the first (0-hour) drug administration on Day 1;
- Subjects fasted for at least 11.5 hours prior to the consumption of the standardized breakfast, and at least 4 hours after, the first drug administration on Days 2-14;
- Subjects fasted for at least 3.5 hours prior to the consumption of dinner.

- Day 15: 130 mg SUBA-Itraconazole administered 30 minutes after the start of a high-fat, high- calorie breakfast

Note: Subjects fasted for at least 4 hours after drug administration.

Treatment B 130 mg SUBA-Itraconazole Fasted

3. Days 1-14: [total dose = 260 mg per day]
    - First dose at 0-hour – 130 mg administered after an overnight fast of at least 10 hours;
    - Second dose at 12-hour – 130 mg administered after having fasted for at least 2 hours.

Notes:

- Subjects fasted for at least 10 hours prior to the first (0-hour) drug administration and continued to fast for at least 4 hours after the first drug administration;
- Subjects fasted for at least 2 hours prior to the second (12-hour) drug administration until at least 1.5 hours after the second drug administration.

- Day 15: 130 mg administered after an overnight fast of at least 10 hours

Note: Subjects fasted for at least 4 hours after drug administration**.**

Food Administration: High Fat, High Calorie Breakfast

Two eggs (fried in butter)
Two strips of bacon
Two slices of white toast with 10 g butter (2 pats)
4 oz hash brown potatoes
8 oz full-fat milk
The meal contained approximately:
Protein calories 133

Reference ID: 4360457

Carbohydrate calories 260
Fat calories 526

Bioanalytical Procedures
Subject plasma concentrations of itraconazole were measured according to a liquid chromatographic (LC) tandem mass spectrometric detection (MS/MS) achiral method (PMRI-1665-16) developed and validated at the Bioanalytical Laboratory (b) (4) The standard calibration range was from 25-2000 ng/mL for Itraconazole using a plasma sample volume of 0.200 mL.

Reviewer Comment: The assay validation results were found to be acceptable by the reviewer with intra-day precision of <10% and accuracy of 84-96%%. The inter-day precision and accuracy were also acceptable at <10% and 89%, respectively. Stability of processed samples were demonstrated for 3 hours at room temperature and 56.75 hours at 5°C.

PHARMACOKINETIC RESULTS:
Pharmacokinetic and Statistical Dataset
Subjects from whom the estimation of Cmax,ss, Ctrough, and AUCtau parameters (on Day 15) was possible for both periods and who complied with all protocol requirements were included in the PK and statistical dataset. Data from subjects in this dataset were used for the PK and statistical analyses. The dataset was defined prior to the assay of samples.

Four (4) subjects discontinued participation from the study prior to Period 2 dosing. As such, these subjects did not accrue sufficient data for the estimation of Cmax,ss, Ctrough, and AUCtau parameters from both periods, and were therefore not included in the PK and statistical analyses. Accordingly, 20 subjects were included in PK and statistical dataset.

The results of the PK and statistical analyses for itraconazole are presented in Table 1.

Table 1. Summary of PK Results for Itraconazole

Based on Statistical Dataset								
Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
C_{max_ss}	A	20	1519.1 (43)	1403.1	A vs B	73.05	69.01 - 77.33	10
(ng/mL)	B	20	2085.2 (43)	1920.7				
C_{trough}	A	20	1071.5 (36)	1008.7	A vs B	91.53	86.41 - 96.96	10
(ng/mL)	B	20	1218.5 (51)	1102.1				
AUC_{tau}	A	20	14183.2 (35)	13370.0	A vs B	78.09	74.49 - 81.86	9
(hr*ng/mL)	B	20	18479.8 (44)	17122.2				

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Treatment A (Test) Fed: SUBA-Itraconazole 65 mg Capsules (2 capsules on Days 1-14 BID, Day 15 QD),
Treatment B (Reference) Fasted: SUBA-Itraconazole 65 mg Capsules (2 capsules on Days 1-14 BID, Day 15 QD)

SPONSOR'S CONCLUSIONS:
Overall, the test product demonstrated modestly lower total and peak exposure and relatively similar concentrations of itraconazole at the end of the dosing interval when administered under fed conditions compared to the fasted state (fed/fasted ratios of 78.09% for AUC_{tau}, 73.05% for Cmax,ss and 91.53% for C_{trough}).

The 90% CI of the relative mean plasma itraconazole AUC_{tau} of the drug product under fed versus fasted conditions was not between 80.00 and 125.00%. (74.49 - 81.86%) and the 90% CI of the relative mean plasma itraconazole Cmax,ss of the drug product under fed versus fasted conditions was not between 75.00 and 125.00% (69.01 - 77.33%). Therefore, it is not possible to declare the absence of a food effect on SUBA-itraconazole 65 mg Capsule upon twice daily administration of two capsules (2×65 mg) on Days 1-14 and one administration of two capsules (2×65 mg) on Day 15, in healthy, adult, human subjects. The administration of SUBA-Itraconazole 65 mg Capsules was generally well- tolerated by the healthy subjects participating in this study. All TEAEs were mild in severity. No SAEs were reported in the conduct of this study and none of the TEAEs had a significant impact on the safety of the subjects or on the integrity of the study results.

Reviewer's Conclusions/Comments:

- The SUBA Itraconazole 65 mg product demonstrated a significant food effect given that the systemic exposure, as given by the geometric mean ratios for AUC and C_{max} of itraconazole, which were respectively, 22% and 27% lower, when 130 mg (2 x 65 mg) was administered BID under fed conditions at steady-state, as compared to when the same dosage regimen was given under fasted conditions.
- The 90% CI's for steady-state itraconazole AUC and C_{max} were below the 80 to 125% acceptance margin when SUBA-Itraconazole was given at 130 mg BID under fed conditions.

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Office of Clinical Pharmacology:
Pharmacometric review

Summary of Findings

The pharmacometric review focused on assessing the population PK analysis of itraconazole for SUBA-itraconazole and Sporanox formulations that include single and multiple doses of SUBA-itraconazole 65 mg capsules in healthy adult subjects. Exposure-response relationship between itraconazole exposure and safety was also explored. Key conclusions are:

- The exposure of SUBA-itraconazole was slightly higher than the reference drug Sporanox;
- SUBA-itraconazole has less variability in exposure (AUC, C_{max}) than Sporanox, which equates to an approximate 30-35% reduction in exposure variability for SUBA compared to Sporanox;
- Food decreases itraconazole AUC and C_{max} in both formulations; Food decreases itraconazole AUC_{inf} to 73%, and to decrease C_{max} to 57-64%, which contrasts with the product label for Sporanox;
- Administration of multiple doses increases itraconazole AUC and Cmax in both formulations compared to the administration of a single dose.
- The typical absolute bioavailability (median, 90% confidence interval) of SUBA-itraconazole after single and multi-dose administration, was estimated to be (0.35, 0.15-0.61) and (0.87, 0.69-0.94), respectively, and the absolute bioavailability for Sporanox after single- and multi-dose administration was estimated to be (0.20, 0.08-0.41) and (0.51, 0.32-0.66), respectively.
- The absolute SUBA-itraconazole/Sporanox bioavailability median ratio was 175% (0.35/0.20) and 170% (0.87/0.51) after single and multi-dose administration, respectively.
- There was no clear exposure-response relationship for safety at the doses and tested duration (15 days) evaluated in the studies in healthy subjects.
- From the pharmacometric perspective, the 65 mg dose of SUBA is acceptable for the proposed indications. It is anticipated that the SUBA 65 mg dose will deliver itraconazole exposure that is as effective as Sporanox. However, since safety data were from healthy subjects, there remains uncertainties in safety when using the SUBA-itraconazole formulation in patients.

Key Review Questions

The purpose of this review is to address the following key questions.

Is the comparability of itraconazole exposure (e.g., AUC_{ss}, C_{max}) in SUBA-itraconazole and Sporanox formulations as demonstrated in population PK analyses support the use of the proposed 65 mg for SUBA-itraconazole?

Yes. While results from population PK analyses and individual Phase 1 PK studies indicate that the overall itraconazole exposure (AUC and C_{max}) in SUBA was slightly higher than that in

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Sporanox, the exposure to itraconazole after administration of SUBA-itraconazole was within the range achieved in Sporanox formulation.

As shown in **Table 1**, the AUC and Cmax for the 65 mg SUBA-itraconazole dose were above the reference 100 mg Sporanox dose after single- and multi-dose administration. In the single dose setting, predicted itraconazole AUC_{inf} of SUBA were 112.6% and 119.6% of Sporanox under fasted and fed status, respectively; and predicted itraconazole C_{max} were 126.7% and 120.8% of Sporanox under fasted and fed status, respectively. Food decrease itraconazole in both formulations (Figure 1). The population effect of food was to decrease the AUC_{inf} and AUC_{0-72} of itraconazole to 73-82% of that in the fasted state, and to decrease C_{max} to 57-64 % of that in the fasted state.

In the multi-dose settings, the differences between the formulations were larger in the multi-dose setting due to the impact of the higher concentrations on non-linear metabolism of the drug (**Figure 2**). The median AUC_{0-72} was 153% and 131% of the reference after once and twice daily administration of two capsules (2×65 mg) under fed condition, respectively. And the median C_{max} was 139% and 124% of the reference after once and twice daily administration of two capsules (2×65 mg), respectively (**Table 1**).

While SUBA has higher median AUC and C_{max} values than the reference drug, the variability in exposure was less for SUBA-itraconazole (CV% for AUC_{0-72} and Cmax of ~41% and 46%, respectively) than Sporanox (CV% for AUC_{0-72} and C_{max} of ~63% and~66%, respectively). This amounts to an approximate 30-35% reduction in exposure variability for SUBA-itraconazole compared to Sporanox. The exposure of SUBA-itraconazole was covered by the exposure range of Sporanox. The ratio of 95th to 5th percentile of AUC and C_{max} was less in SUBA-itraconazole than Sporanox, and the upper bound of 90% CI of AUC and C_{max} for SUBA-itraconazole was less than that of Sporanox. As such the slightly higher median or mean exposure in SUBA may not be a serious concern from exposure perspective.

Table 1: Predicted Median Itraconazole Exposure after Single and Multi-dose of Sporanox and SUBA-itraconazole

		SUBA 65 mg		Sporanox 100 mg		% of Sporanox	
		AUC_{inf}	C_{max}	AUC_{inf}	C_{max}	AUC_{inf}	C_{max}
Single Dose	Fed	750	43.6	627.1	36.1	119.6	120.8
	Fasted	962	75.9	854.5	59.9	112.6	126.7
	Fed/Fasted(%)	78.0	57.4	73.4	60.3		
Multi-dose Two capsules	Fed (once daily) Fed (twice daily)	12171* 85658*	411 1615	7924 65230	295.1 1307	153.6* 131.3*	139.2 123.6

Note: * value was for AUC_{0-72} multi-dose.

Source: Adapted from Table 18 on page 104 and Table 19 on page 108 of Applicant's population PK report

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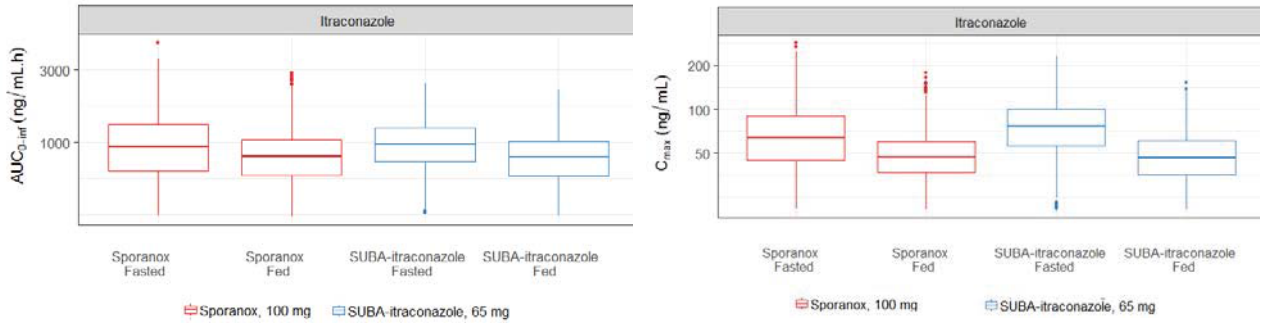
Figure 1: Predicted Itraconazole AUC_{inf} and C_{max} after Single Dose of Sporanox and SUBA-itraconazole under Fed and Fasting Conditions

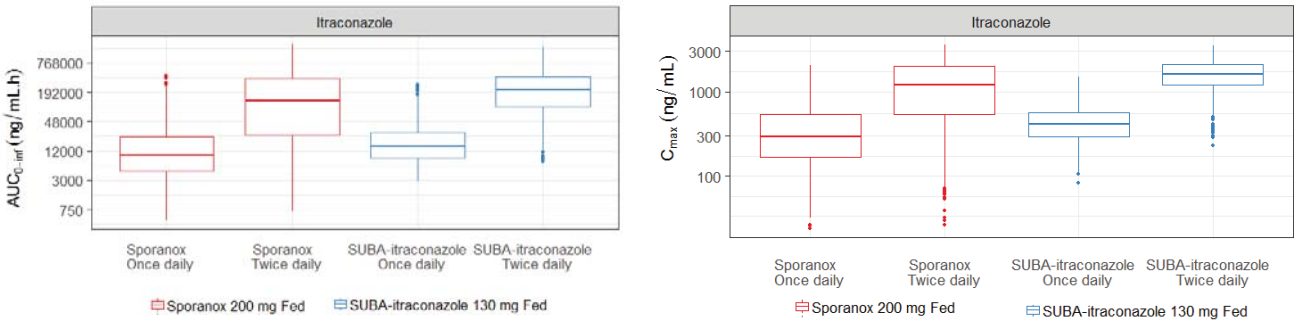
AUC_{inf} (ng/mL·h) **C_{max} (ng/mL)**



Source: Adapted from Figure 53 on page 102 of Applicant's population PK report

Figure 2: Predicted Itraconazole AUC_{inf} and C_{max} after Once-daily and Twice Daily of Multi-dose of 200 mg Sporanox and 130 mg SUBA-itraconazole for 15 Days

AUC_{inf} (ng/mL·h) **C_{max} (ng/mL)**



Source: Adapted from Figure 55 on page 110 of Applicant's population PK report

Does the exposure-response relationship of itraconazole for safety support the use of multiple doses of 65 mg SUBA?

Yes. No exposure-response relationship for AEs was identified by the applicant and the reviewer based on exposure and safety data from healthy volunteers after multiple doses of SUBA-itraconazole for 15 days. However, this result should be explained with caution because safety data in patients are not available, and the exposure-safety relationship may be different between patients and healthy volunteers. Please see reviewer's analysis below for details.

The applicant explored the relationship between itraconazole systemic exposure from SUBA-itraconazole 65 mg capsules and safety events using data in multi-dose studies MPG012, MPG015, and MPG017 where SUBA-itraconazole and the reference drug were used for 15 days.

Study MPG012 was an open label, randomized, two-treatment, two-sequence, two-period, crossover, multiple-dose, steady-state, oral bioequivalence study of SUBA-Itraconazole

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Capsules 65 mg [2 X 65 mg] (Test) and Sporanox (Itraconazole) Capsules 100 mg [2 X 100 mg] (Reference) in healthy, adult, human subjects under fed conditions. 21 subjects (13 female, 8 male) completed the Study. In each dosing period, following breakfast, an oral dose of two capsules of study drug (SUBA-Itraconazole 65 mg Capsules or Sporanox 100 mg Caspules) was administered once daily for 14 consecutive days. Mean itraconazole exposure for group with AE versus no AE were compared in **Table 2**. This table lists the subjects from Study MPG012 with their respective AUCt and Cmax measurement at steady state and whether they experience an AE or not while taking SUBA itraconazole 65 mg Capsules. There was no evident difference in mean C_{max} and steady state AUC between the two groups.

Table 2: Study MPG012-Mean Itraconazole Exposure for Group with AE vs no AE

AE	# Observations	Variable	N	Mean	Std Dev	Minimum	Maximum
>=1 AE	7	$C_{max,ss}$ (ng/ml)	7	600.7	178.4	408.7	917.0
		$AUC_{t\ ss}$ (hr. ng/ml)	7	8417.2	1553.3	6438.4	11507.6
No AE	13	$C_{max,ss}$ (ng/ml)	13	594.9	181.8	293.4	903.2
		$AUC_{t\ ss}$ (hr. ng/ml)	13	8249.9	3433.8	3531.7	13744.3

Source: Table 13 on page 20 of Summary of Clinical Safety Report

Study MPG015 was to evaluate the bioequivalence between SUBA-itraconazole 65 mg Capsules and Sporanox 100 mg following multiple-dose administration for 15 days in healthy, adult, nonsmoking subjects, under fed conditions A total of 24 subjects started the study, with 16 subjects completing the study; 20 subjects (9 female and 11 male) contributed data to the Treatment A arm, 22 subjects (9 female, 13 male) to Treatment B.

Mean itraconazole exposure for group with AE versus no AE were compared in **Table 3**. This table lists the subjects from Study MPG015 with their respective AUCt and C_{max} measurement at steady state and whether they experienced an AE or not while taking SUBA-itraconazole 65 mg Capsules. The group with AE reported does not have higher exposure than the group with no AE, suggesting that no exposure-response relationship was revealed.

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Table 3: Study MPG015-Mean Itraconazole Exposure for Group with AE vs no AE

AE	# Observations	Variable	Mean	Std Dev	Minimum	Maximum
>=1 AE	6	$C_{max,ss}$ (ng/ml)	1516.7	232.4	1110.0	1810.0
		$AUC_{t\ ss}$ (hr. ng/ml)	13771.0	2396.4	9339.8	16275.0
No AE	10	$C_{max,ss}$ (ng/ml)	1758.0	418.2	1210.0	2650.0
		$AUC_{t\ ss}$ (hr. ng/ml)	17261.1	3810.0	12497.0	24417.5

Source: Table 13 on page 20 of Summary of Clinical Safety Report

Study MPG017 was to evaluate the effect of food on SUBA-itraconazole 65 mg Capsules following multiple-dose administration in healthy, adult, nonsmoking subjects, under fed conditions for 15 days. A total of 24 subjects started the study, with 20 subjects (3 Female, 20 male) completing the study. In each period, subjects were confined to the clinical facility from 10.5 hours prior to dosing until after the 24-hour post-dose blood draw on Day 15. In each period, subjects were administered two capsules (2×65 mg) of SUBA-itraconazole 65 mg Capsules (Mayne Pharma International Pty Ltd, Australia) twice daily (12 hours apart) on Days 1-14 and once on Day 15 under fasted or fed conditions.

Mean itraconazole exposure for group with AE versus no AE were compared in **Table 4** below lists the subjects from Study MPG017 with their respective AUCt and C_{max} measurement at steady state and whether they experienced an AE or not while taking SUBA-itraconazole 65 mg Capsules. The group with AE reported has comparable exposure to the group with no AE, suggesting that no exposure-response relationship for AEs in this study.

Table 4: Study MPG017-Mean Itraconazole Exposure for Group with AE vs no AE

AE	# Observations	Variable	Mean	Std Dev	Minimum	Maximum
>=1 AE	9	$C_{max,ss}$ (ng/ml)	1622.2	717.0	570.0	2910.0
		$AUC_{t\ ss}$ (hr. ng/ml)	14926.4	5573.1	6197.5	25680.0
No AE	11	$C_{max,ss}$ (ng/ml)	1434.7	611.4	862.0	3040.0
		$AUC_{t\ ss}$ (hr. ng/ml)	13575.2	4734.1	7763.5	23982.5

Source: Table 17 on page 26 of Summary of Clinical Safety Report

Independent analysis was conducted by the pharmacometrics reviewer to explore the relationship between itraconazole exposure from SUBA and AEs by combining exposure and AE data from studies MPG012, MPG015, and MPG017. A logistic regression analysis was used as

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shown in Section 3. Similar to the conclusion from the sponsor, no clear exposure-response relationship for safety in healthy adult subjects were revealed.

Please note, the relationship between exposure and safety should be explained with caution. The safety information here was from healthy volunteers and the tested duration was limited to two weeks. Whether the exposure-response relationship for safety is the same as in healthy volunteers is unknown.

Results of Sponsor's Analysis

The Applicant submitted a population PK modeling and simulation report entitled "*Population In Vitro-In Vivo Pharmacokinetic Model of Itraconazole and hydroxyl-itraconazole for SUBA-itraconazole and Sporanox Formulations including SUBA-itraconazole 65 mg Capsules"*. The study developed an model to derive final PK parameter values and estimate the itraconazole exposure (AUC C_{max}) for both formulations. The exposure was compared between two formulations under fed-fasted state and after single and multiple doses.

Population PK Analysis

Objectives: 1) The primary objective of this analysis was to: i) develop a pharmacokinetic model that describe the accumulation kinetics of itraconazole and hydroxy-itraconazole (first-pass metabolism and disposition);ii) identify covariates that are predictive of the pharmacokinetic behavior of itraconazole with particular reference to the variability of the oral absorption process, the influence of fed or fasted state on absorption, and the impact of co-administration of omeprazole; iii) Compare the itraconazole exposure for SUBA- and Sporanox formulations for various dosing scenarios.

Data: The population PK analysis included oral pharmacokinetic data pooled from 12 Phase 1 single-and multi-dose randomized crossover design studies comparing Sporanox with SUBA-itraconazole. Summary of clinical studies included in the analysis is shown in **Table 5**. A total of 36069 plasma concentrations (average of approximately 106 observations per subject) from 340 subjects were in the population PK dataset. Summary of demographics are shown in Table 6.

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Table 5: **Clinical Studies Comparing SUBA-itraconazole with Sporanox in the Fed and Fasted States**

Study	Number of subjects	Single/ Multiple	Treatment periods per subject	SUBA-itraconazole daily doses per subject	Sporanox daily doses per subject	Fed (Yes/No)	Fasted (Yes/No)
HGN007	36	Single	4	1 x 50 mg/2 periods	1 x 100 mg/2 periods	Y	Y
HGN008	48	Single	4	1 x 50 mg/2 periods	1 x 100 mg/ 2 periods	Y	N
MPG009	52	Single	4	1 x 65 mg/2 periods	1 x 100 mg/2 periods	Y	Y
10850702	24	Single	4	1 x 50 mg/ 1 period 2 x 50 mg/ 1 period	1 x 100 mg/ 1 period 2 x 100 mg/ 1 period	N	Y
10850703	36	Single	4	1 x 50 mg/2 periods	1 x 100 mg/2 periods	Y	Y
MPG016	29	Single	2	2 x 65 mg/1 period 2 x 65 mg with 40 mg omeprazole/1 period	N	N	Y
10850705	24	Multiple	2	2 x 50 mg q.d x 15 days/1 period	2 x 100 mg q.d x 15 days/ 1 period	Y	N
10850706	24	Multiple	2	2 x 50 mg b.i.d x 15 days/1 period	2 x 100 mg b.i.d x 15 days/ 1 period	Y	N
MPG012	22	Multiple	2	2 x 65 mg q.d x 15 days/1 period	2 x 100 mg q.d x 15 days/1 period	Y	N
MPG013	15	Multiple	2	2 x 65 mg t.i.d x 3 days and q.d on day 4/1 period	2 x 100 mg t.i.d x 3 days and q.d on day 4/1 period	Y	N
MPG015	16	Multiple	2	2 x 65 mg b.i.d x 15 days/1 period	2 x 100 mg b.i.d x 15 days/1 period	Y	N
MPG017	20	Multiple	2	2 x 65 mg b.i.d x 15 days/1 period	N	Y	Y

All studies were randomized cross-over design studies with 2 or 4-treatment periods per subject.
q.d: once daily, b.i.d: twice daily, t.i.d: three times daily.

Source: Table 2 on page 25 of Applicant's population PK report

Table 6: Demographic Characteristics of Study Population in Single versus Multi-Dose Studies

Demographic	Single-dose studies	Multi-dose studies	All studies
n	224	116	340
Age (years)	34.9 (34, 18-59)	38.5 (36.5, 19-67)	36.1 (35.5, 18-67)
Weight (kg)	75.9 (75.7, 47.4-110.7)	82.4 (83.2, 53.5-109.5)	78.1 (78, 47.4-110.7)
Height (cm)	173.6 (174.9, 147.7-198.1)	174.4 (174.9, 155-198.1)	173.9 (174.9, 147.7-198.1)
Body mass index(kg/m^2)	25 (25.4, 18-30)	26.9 (27.3, 18.3-32.7)	25.7 (25.9, 18-32.7)
Sex (Male:Female)	162:62	77:39	239:101
Race (White: Black/African American/Other)	155:39:30	37:53:26	192:9
Ethnicity (Hispanic: not Hispanic)	16:208	5:111	21:319

All values calculated as mean (median, range) unless stated otherwise. n is the number of subjects

Source: Table 8 on page 47 of applicant's population PK report

Methods:

Software: Modelling was performed using a Dell® Power Edge R910 server with 4x10 core Xeon 2.26 Ghz processors running Windows Server 2008 R2 Enterprise 64-bit. Log-transformed plasma concentrations were used for pharmacokinetic modelling. Model development employed nonlinear mixed effect modelling using NONMEM (Version 7.3; ICON Development Solutions, Ellicott City, MD).

Population PK Model

Structure Model of the Intravenous Literature Data: The sponsor first built a model for intravenous infusion data in literature. Intravenous data were best described using a 3-compartment model for ICZ and 1 compartment model for HICZ. The clearance of HICZ was best described using non-linear (Michaelis-Menten) elimination kinetics while the clearance of ICZ was best described using a mixed inhibition model that allowed the metabolite to inhibit the

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metabolism of the parent drug (i.e. the metabolite inhibiting its own formation). Residual variability models of ICZ and HICZ were best described using proportional error model. The structural model provided satisfactory description of ICZ and HICZ data and was then extended to include the oral data.

Intravenous-oral population model: The base model for the combined intravenous-oral data was based on the previously published first pass model which was based on data from 7 out of the 11 clinical studies included in the updated model. The published first-pass model was updated herein using all available data from the 11 clinical studies. The published first-pass metabolism model had the following covariate effects in its final model: a scale factor on the central volume of distribution for the oral data; allometric scaling of *Qh,plasma*, a covariate effect parameter of multi-dose studies on the logit-transform fraction absorbed parameter (*LGTFabs*), an effect of fed status on *LGTFabs* and absorption rate constant (*Ktr*), and an effect of formulation on *LGTFabs*. These covariates were retained as significant in the updated model after including all the available pharmacokinetic data for Sporanox and SUBA-itraconazole from the 11 studies combined.

A 3-compartment model with 4-transit absorption compartments was the best model to describe the combined intravenous-oral data. The selection of the transit absorption model was based on a previous population pharmacokinetic analysis of Sporanox and SUBA-itraconazole data by the same authors. The elimination kinetics of ICZ and HICZ were described by the elimination model of the intravenous data described above. Residual variability models of oral ICZ and HICZ were best described using a proportional model for the single-dose oral studies, and a combined proportional and additive model for the multi-dose oral studies. A schematic representation of the compartmental structure of the intravenous-oral data of ICZ and HICZ is shown in **Figure 7**. The final estimated population pharmacokinetic parameters for all fixed and random effects in the final ICZ and HICZ model are presented in **Table 7**. The standard goodness-of-fits plots of the oral ICZ concentrations across single and multi-dose studies are presented in **Figure 3**.

The VPC plots for ICZ and HICZ for oral single vs multi-dose data are presented in **Figure 4**.

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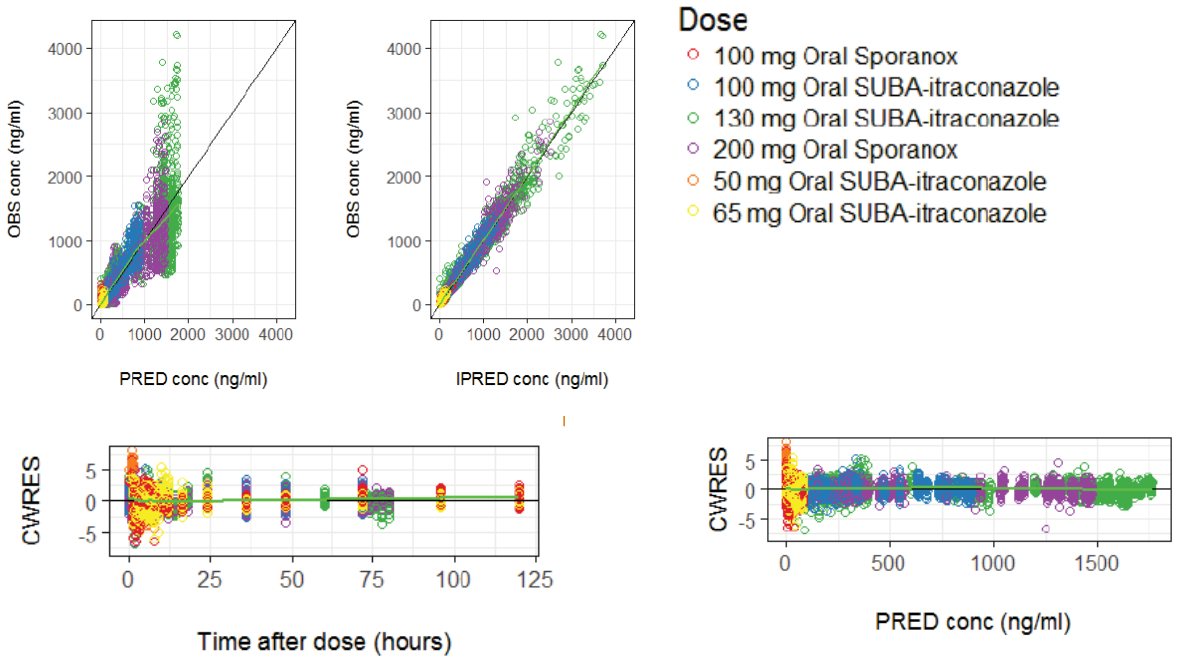
Table 7: Parameter Values for the Final Intravenous-Oral Pharmacokinetic Model

Code	Description	Unit	Pop value[a]	%RSE	BSV (SD)	%RSE	ETA p-value	Shrinkage (%)
$V_{max,ICZ}$	Maximum rate of ICZ metabolism	ng/h	342000	4.1	0.278	3.7	0.848	12
$K_{m,ICZ}$	Concentration at half $V_{max,ICZ}$	ng/ml	6050	4.8	-	-	-	-
V_2	Central volume of distribution-ICZ	L	34.1	4.9	0.354	9.5	0.046	26.3
Q_3	Inter-compartmental clearance (1)- ICZ	L/h	5.43	9.6	-	-	-	-
V_3	Peripheral volume of distribution (1)- ICZ	L	196.1	15.4	-	-	-	-
Q_4	Inter-compartmental clearance (2)- ICZ	L/h	36.9	3.5	-	-	-	-
V_4	Peripheral volume of distribution (2)- ICZ	L	196.1	-	-	-	-	-
$V_{max,HICZ}$	Maximum rate of HICZ metabolism	ng/h	7570	1.8	0.291	3.7	0.649	12.3
$K_{m,HICZ}$	Concentration at half $V_{max,HICZ}$	ng/ml	252	3.1	-	-	-	-
VM	Apparent central volume of distribution-HICZ	L	127	2.9	-	-	-	-
KI	Inhibition constant	ng/ml	320	2.6	-	-	-	-
K_{tr}	Transit absorption rate constant	1/h	2.24	2.8	0.448	3.1	0.989	5.2
$SCLV2$	Scale factor on central volume of distribution of ICZ	Ratio	4.16	7.3	-	-	-	-
$LGTF_{abs}$	Logit-transformed parameter of fraction absorbed	-	-0.164	46.6	0.863	3.5	0.176	17.2
$FORMF_{abs}$	Effect of formulation on fraction absorbed	Ratio	1.22	5.8	-	-	-	-
$FEDK_{tr}$	Effect of fed status on K_{tr}	Ratio	-0.559	2.7	-	-	-	-
$FEDF_{abs}$	Effect of fed status on $LGTF_{abs}$	Ratio	-0.598	11.4	-	-	-	-
$MULTIF_{abs}$-SPO	Effect of multi-dose Sporanox administration on fraction absorbed	Ratio	1.24	4.8	-	-	-	-
$MULTIF_{abs}$-$SUBA$	Effect of multi-dose SUBA-itraconazole administration on fraction absorbed	Ratio	16	2.1	-	-	-	-
$PPICOVV_{max}$	Effect of omeprazole on $V_{max,ICZ}$ and $V_{max,HICZ}$	Ratio	-0.117	27.2	-	-	-	-
$PPICOVF_{abs}$	Effect of omeprazole on F_{abs}	Ratio	1.14	23.8	-	-	-	-
$STUDY705COVV_{max}$	Study 10850705 effect on $V_{max,ICZ}$ and $V_{max,HICZ}$	Ratio	-0.235	12.6	-	-	-	-
$RUVCVIVP$	Proportional residual error-intravenous ICZ	Ratio	0.37	5.7	-	-	-	-
$RUVCVIVM$	Proportional residual error-intravenous HICZ-	Ratio	0.134	9.4	-	-	-	-
$RUVCVSORALP$	Proportional residual error-oral single-dose studies-ICZ	Ratio	0.463	2.4	-	-	-	-
$RUVCVSORALM$	Proportional residual error of oral single studies-HICZ	Ratio	0.451	2.1	-	-	-	-
$RUVCVMORALP$	Proportional residual error of oral multi-dose studies-ICZ	Ratio	0.129	4.7	-	-	-	-
$RUVCVMORALM$	Proportional residual error of oral multi-dose studies-HICZ	Ratio	0.0712	5.8	-	-	-	-
$RUVADDMORALP$	Additive residual error of oral multi-dose studies-ICZ	ng/ml	14.7	38	-	-	-	-
$RUVADDMORALM$	Additive residual error of oral multi-dose studies-HICZ	ng/ml	27	12.2	-	-	-	-

[a] Population typical value. ICZ: itraconazole; HICZ: hydroxy-itraconazole; BSV: between subject variability; SD: standard deviation; %RES: percent of relative standard error

Source: Table 13 on page 66 of Applicant's population PK Modeling report

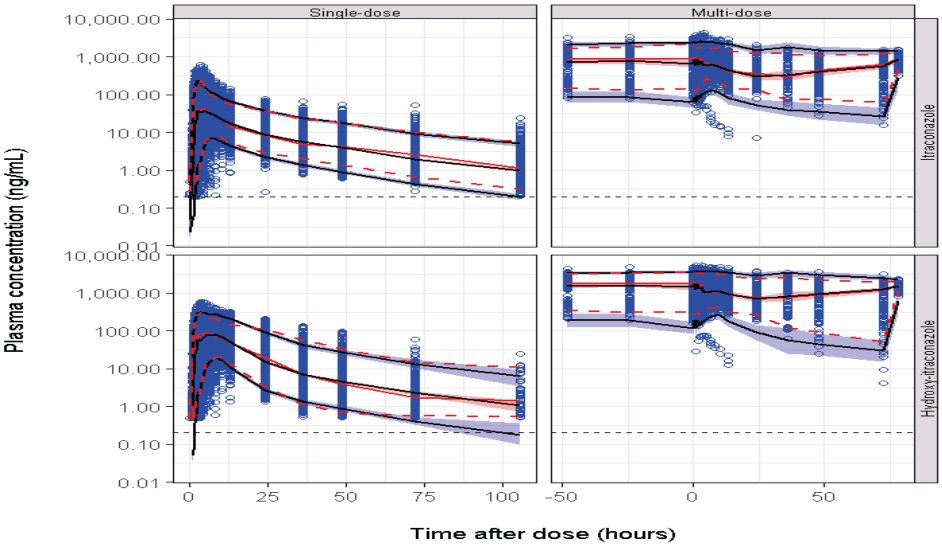
Figure 3: Goodness-of-Fits plots of Oral Itraconazole (Single and Multi-Dose) for the Final Intravenous-Oral Pharmacokinetic Model



Source: Adapted from Figure 21 on page 68 of Applicant's Population PK report

Reference ID: 4360457

Figure 4: Visual Predictive Checks of Oral Itraconazole and Hydroxy-itraconazole SINGLE vs. MULTIDOSE for the Final Intravenous-oral Pharmacokinetic Model

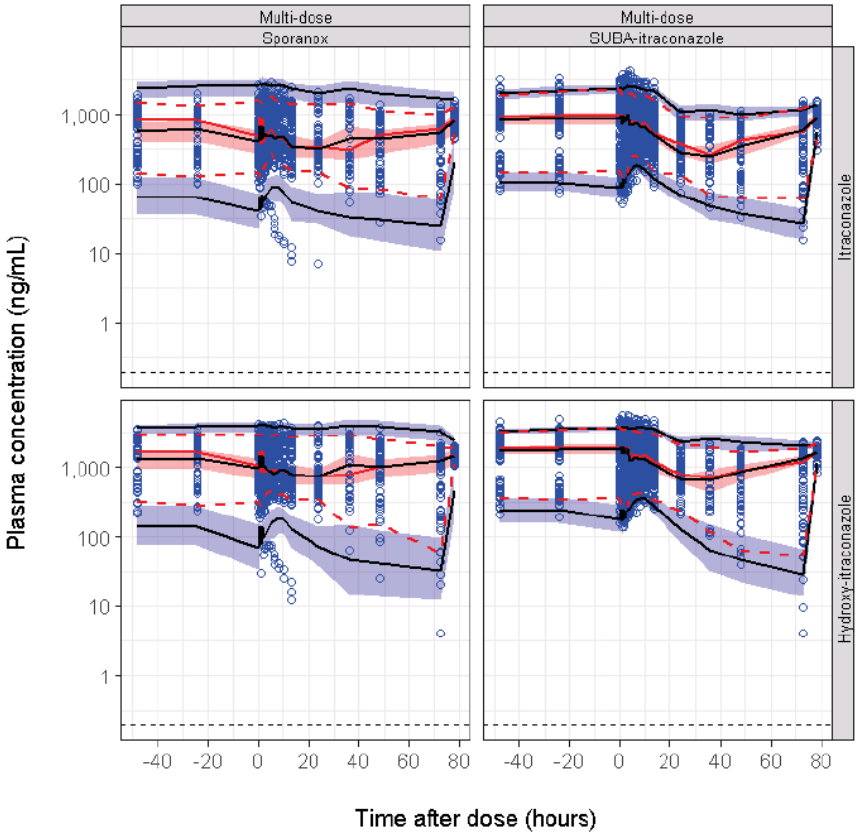


Note: Open circles represent observed itraconazole or hydroxy-itraconazole concentrations. The solid black lines represent the 5th, 50th, and 95th percentiles of the simulated concentrations. The shaded areas represent the 90% confidence interval of the 5th, 50th, and 95th percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations. The dashed red lines represent the 5th and 95th percentiles of the observed concentrations.

Source Figure 24 on page 72 of Applicant's Population PK Report

Reference ID: 4360457

Figure 5: Visual Predictive Checks of Oral Itraconazole and Hydroxy-itraconazole data of MULTI-DOSE Studies Stratified by Formulation for the Final Intravenous-Oral Pharmacokinetic Model

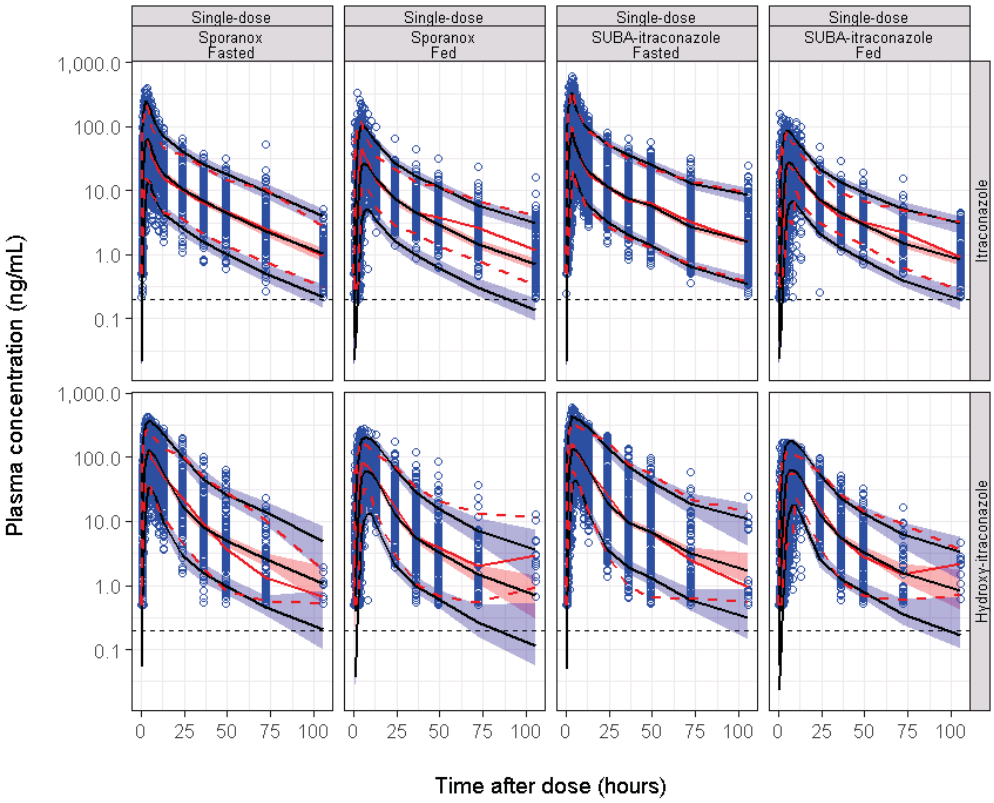


Open circles represent observed itraconazole or hydroxy-itraconazole concentrations. The solid black lines represent the 5th, 50th, and 95th percentiles of the simulated concentrations. The shaded areas represent the 90% confidence interval of the 5th, 50th, and 95th percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations. The dashed red lines represent the 5th and 95th percentiles of the observed concentrations.

Source Figure 25 on page 74 of Sponsor's population PK report

Reference ID: 4360457

Figure 6: Visual Predictive Checks of Itraconazole and Hydroxy-itraconazole of SINGLE-DOSE Studies Stratified by Formulation and Fed Status for the Final Intravenous-oral Pharmacokinetic Model



Note: Open circles represent observed itraconazole or hydroxy-itraconazole concentrations. The solid black lines represent the 5th, 50th, and 95th percentiles of the simulated concentrations. The shaded areas represent the 90% confidence interval of the 5th, 50th, and 95th percentiles of the simulated concentrations. The solid red line represents the median of the observed concentrations. The dashed red lines represent the 5th and 95th percentiles of the observed concentrations.

Source: Figure 26 on page 74 of Applicant's Population PK report

In vitro-in vivo Pharmacokinetic Model

The final intravenous-oral population model was used as a base model to establish an in vitro-in vivo pharmacokinetic model for both Sporanox and SUBA-iraconazole. The *in vitro-in vivo* pharmacokinetic model combined the *in vitro* release models for Sporanox and SUBA-itraconazole, described previously by Abuhelwa *et al*. linked with meta-models of GI pH and GITT. a pH-independent dissolution pathway, representing food solubilizing effects on itraconazole, was added for the fed periods for both formulations Meta-models describing fed and fasted GI pH and GITT were linked to the dissolution models to capture the effect of these physiological variables on the *in vivo* drug release and pharmacokinetics. The meta-models of GI pH and GITT were based on the quantitative meta-analysis models presented by Abuhelwa et al. for stomach, small intestinal, colonic pH and transit times of the multi-unit dosage forms.

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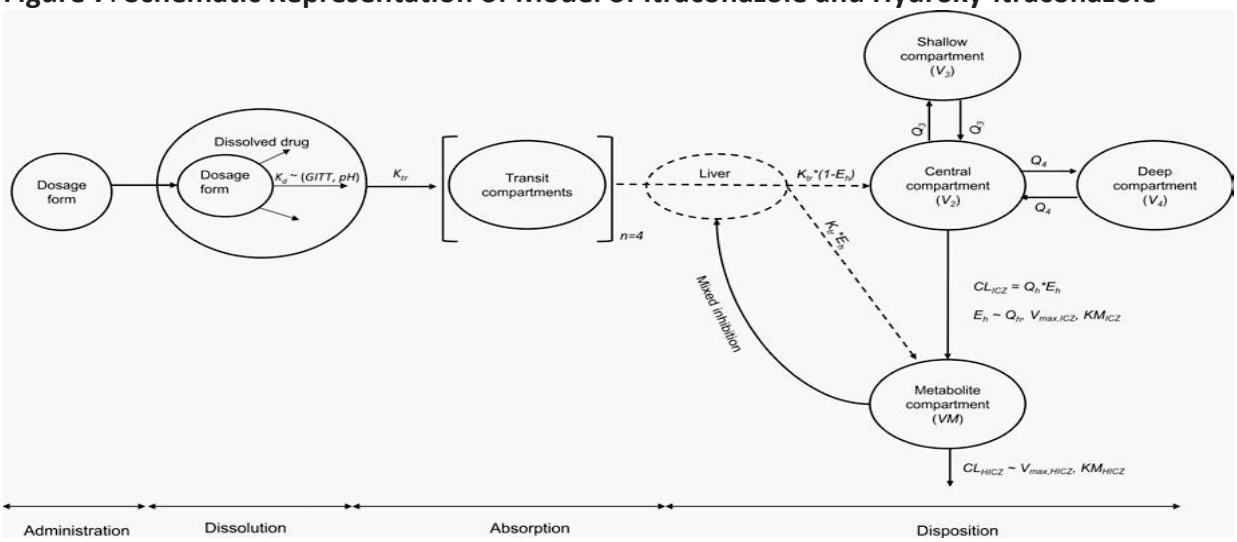
The schematic representation of the compartmental structural model of oral ICZ and HICZ is shown in **Figure 7**. The final model of ICZ kinetics was a 3-compartment model with oral absorption of the dissolved drug described by 4-transit compartments. HICZ kinetics was best described by a 1-compartment distribution model. ICZ clearance was best described using a mixed inhibition model that allowed HICZ concentrations to inhibit the clearance of ICZ (i.e. the metabolite inhibiting its own formation). This elimination model was based on the assumption that HICZ undergoes further metabolism with the same metabolizing enzymes of ICZ and, therefore, may compete and inhibits its own formation. HICZ clearance was best described by Michaelis-Menten elimination kinetics (non-linear accumulation). The final population PK parameters are summarized in **Table 8**.

Figure 7: **Schematic Representation of Model of Itraconazole and Hydroxy-itraconazole**



Kd is the pH-dependent dissolution rate; GITT is Gastrointestinal transit time. Refer to Table 13 for definition of the rest of the parameters. To ensure that the peripheral volume of distributions (V3, V4) were bigger than the central volume, the peripheral volumes were estimated additive to the previous volume (i.e. V3 = V2 + ϑ1; and V4 = V3 + ϑ2) where ϑ is an additive estimated parameter.

Table 8: Comparison of Parameter Estimates from the Model and Intravenous-Oral Model

Model			*IVIVC* model		Intravenous-oral model	
Code	**Description**	**Unit**	**Pop value**	**%RSE**	**Pop value**	**%RSE**
K_{tr}	Transit absorption rate constant	1/h	2.84	0.3	2.24	2.8
$PPICOVF_{abs}$	Effect of omeprazole on F_{abs}	Ratio	1.06	17.5	1.14	23.8
$MULTIF_{abs}$-SPO	Effect of multi-dose Sporanox administration on fraction absorbed	Ratio	1.5	0.2	1.24	4.8
$MULTIF_{abs}$-SUBA	Effect of multi-dose SUBA-itraconazole administration on fraction absorbed	Ratio	16	9.4	16	2.1
K_{d2}-Sporanox	pH-independent pathway dissolution parameter for Sporanox	1/h	1.24	3.3	-	-
K_{d2}-SUBA-itraconazole	pH-independent pathway dissolution parameter for SUBA itraconazole	1/h	0.0104	11.6	-	-
BSV-K_{tr} (% shrinkage)	Between subject variability on K_{tr}	SD	0.499	2.4 (2.3)	0.448	3.1 (5.2)

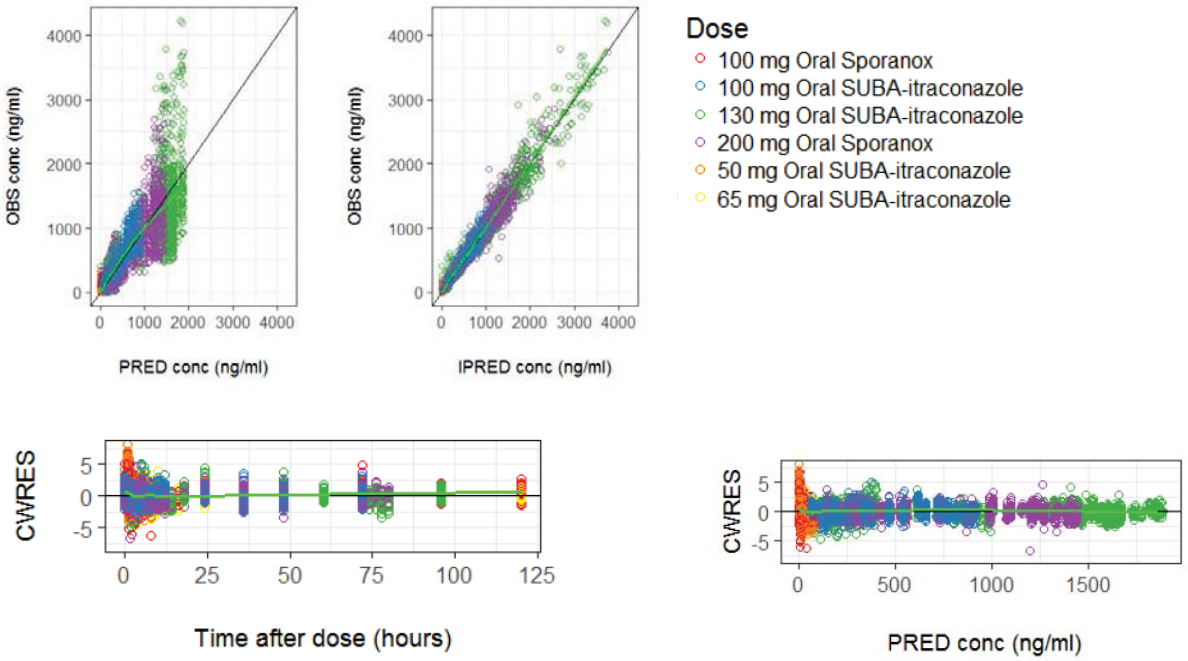
RSE: relative standard error; SD: standard deviation; Pop value: population value

Source: Table 8-1 on page 13 of applicant's Population PK report

Reference ID: 4360457

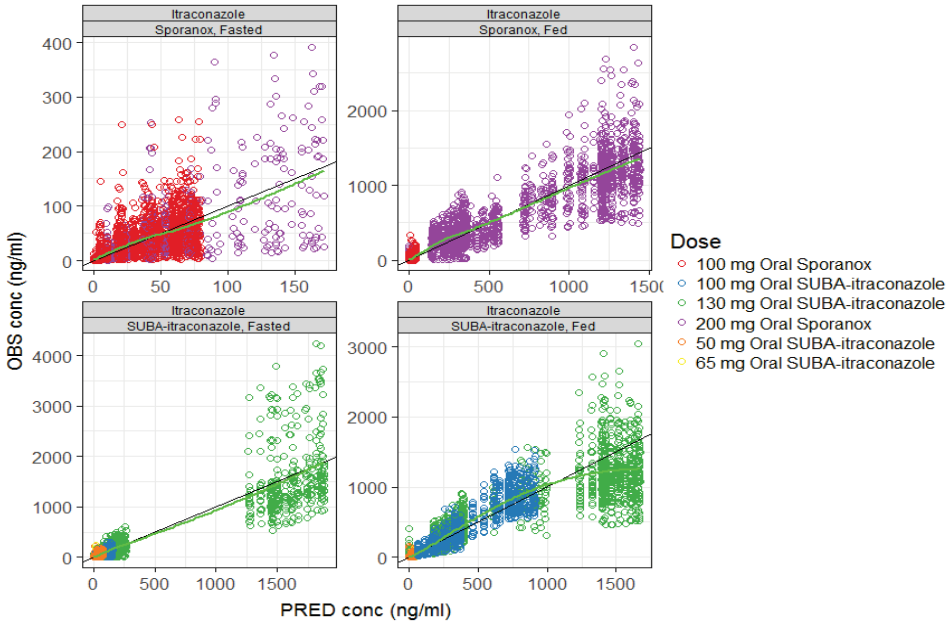
Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs). The goodness-of-fit plots for the final model are displayed in **Figure 8** and **Figure 9** and the VPCs plots are demonstrated in **Figure 10**.

Figure 8: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Adapted from Figure 32 on page 82 of Applicant's Population PK report

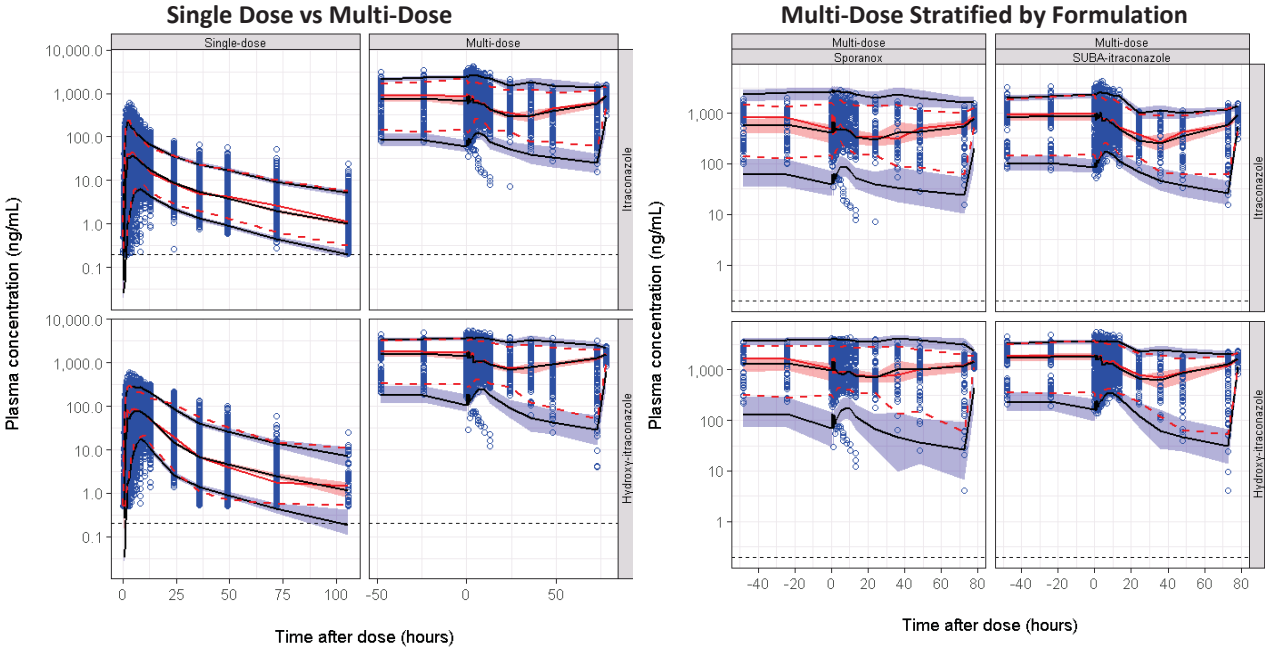
Figure 9: Final Model: Observed vs. Individual Predicted Itraconazole Concentrations Stratified on Formulation and Fed Status.



Reference ID: 4360457

Source: Figure 33 on page 83 of Applicant's Population PK report

Figure 10: Prediction-Corrected Visual Predictive Checks for the Final Model



Source: Adapted from Figure 39 and Figure 40 on page 90-91 of Applicant's Population PK report

Simulations: Simulations were conducted using the final model and final parameter values to investigate the effect of food on predicted ICZ and HICZ exposure, and to compare the exposure of 100 mg Sporanox versus the 65 mg SUBA-itraconazole after single and multi-dose (steady state) administration scenarios. Predicted food effects on the exposure of itraconazole for single dose 100 mg Sporanox and 65 mg SUBA-itraconazole are summarized in **Table 9**. Predicted itraconazole on Day 15 of multi-dose 200 mg Sporanox and 130 mg SUBA-itraconazole is summarized in **Table 10**.

Table 9 : Predicted Food Effects on the Exposure of Itraconazole for Single Dose 100 mg Sporanox and 65 mg SUBA-Itraconazole

Metric	Formulation	Dose	Fed status	median	Percent of Sporanox	gmean	Percent of Sporanox	mean	%CV	95% CI
AUC_{0-72} (ng/ml*h)	Sporanox	100 mg	Fasted	728.5		682 3		830.6	59.4	(212.9-1710.7)
		100 mg	Fed	566		528.4		682.4	67	(128.4-1543.2)
			Fed/fasted(%)	77.7		77.4		82 2		
	SUBA-itraconazole	65 mg	Fasted	883.3	121.2	837	122.7	904.7	37.6	(390.9-1493.2)
		65 mg	Fed	687	121.4	644.7	122.0	719 3	43.8	(255.8-1291.4)
			Fed/fasted(%)	77.8		77.0		79 5		
AUC_{inf} (ng/ml*h)	Sporanox	100 mg	Fasted	854.5		794 2		963.4	59.5	(246.4-1972.9)
		100 mg	Fed	627.1		581 3		754 2	68	(139.1-1712.1)
			Fed/fasted(%)	73.4		73.2		78 3		
	SUBA-itraconazole	65 mg	Fasted	962	112.6	917.4	115.5	995 5	38.9	(418.2-1654)
		65 mg	Fed	750	119.6	708 9	122.0	794.4	45	(274.4-1435.5)
			Fed/fasted(%)	78.0		77.3		79.8		
C_{max}(ng/ml)	Sporanox	100 mg	Fasted	59.9		55.1		68	61.7	(16.2-145)
		100 mg	Fed	36.1		33.3		43.4	69.4	(8-99.9)
			Fed/fasted(%)	60.3		60.4		63.8		

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Metric	Formulation	Dose	Fed status	median	Percent of Sporanox	gmean	Percent of Sporanox	mean	%CV	95% CI
	SUBA-itraconazole	65 mg	Fasted	75.9	126.7	73.1	132.7	80 5	42.4	(31.9-141.3)
		65 mg	Fed	43.6	120.8	41.3	124.0	47 1	49.3	(15.6-87.7)
			Fed/fasted(%)	57.4		56.5		58 5		
$T_{max\ (h)}$ (hour)	Sporanox	100 mg	Fasted	3.5		3.6		3 9	61.4	(2-6)
		100 mg	Fed	6		6 3		6.7	41.2	(3.5-12)
			Fed/fasted(%)	171.4		175.0		171.8		
	SUBA-itraconazole	65 mg	Fasted	3.5	100.0	3 3	91.7	3 5	40	(1.5-6)
		65 mg	Fed	6	100.0	5.7	90.5	6 2	46.4	(3-12)

Source: Adapted from Table 18 on page 104 of Sponsor's population PK report

Table 10: Predicted Itraconazole Exposure on Day 15 of Multi-dose 200 mg Sporanox and 130 mg SUBA-itraconazole

Metric	Regimen	Formulation	Dose	Fed status	median	Percent of Sporanox	gmean	Percent of Sporanox	mean	%CV	95% CI
AUC_{0-72} (ng/ml*h)	Once daily	Sporanox	200 mg	Fed	7923.9		8389.9		14087.6	113.4	(1663.8-
		SUBA-itraconazole	130 mg	Fed	12170.8	153.6	12366.4	147.4	15652.3	73.6	(4192.8-
	Twice daily	Sporanox	200 mg	Fed	65229.9		45281.3		79428.2	84.7	(3677.7-
		SUBA-itraconazole	130 mg	Fed	85657.8	131.3	76705.8	169.4	88906.8	47.8	(22953.2-
C_{max} (ng/ml)	Once daily	Sporanox	200 mg	Fed	295.1		289.8		395.5	82	(70.6-1043.3)
		SUBA-itraconazole	130 mg	Fed	410.7	139.2	409.2	141.2	457.2	48.3	(181.5-878.5)
	Twice daily	Sporanox	200 mg	Fed	1306.7		1001.4		1473.6	73.4	(135.3-3467.4)
		SUBA-itraconazole	130 mg	Fed	1615.4	123.6	1530	152.8	1665.2	38.2	(694.1-2749.2)
T_{max} (hour)	Once daily	Sporanox	200 mg	Fed	6		6.4		6.8	37.9	(3.5-12)
		SUBA-itraconazole	130 mg	Fed	6	100.0	5.8	90.6	6.2	43.6	(3-12)
	Twice daily	Sporanox	200 mg	Fed	6		6.1		6.5	32.9	(3.5-10)
		SUBA-itraconazole	130 mg	Fed	6	100.0	5.5	90.2	5.9	37.6	(3-10)

Source: Adapted from Table 19 on page 108 of Sponsor's population PK report

Comparison of Exposure of 100 mg Sporanox vs. 65 mg SUBA-itraconazole*:*

Single Dose Administration*:* The population model predicted itraconazole concentrations for the 65 mg SUBA-itraconazole dose were found to be above the reference 100 mg Sporanox dose.

Table 9 shows a summary of ICZ and HICZ exposure for SUBA-itraconazole 65 mg and Sporanox 100 mg administered in the fed and fasted states. The values for SUBA-itraconazole are expressed as a percentage of the values for the equivalent reference dose. In the fasted state, the median ICZ AUC_{inf} for SUBA-itraconazole was 113% of the reference dose. In the fed state, the median AUC_{inf} for SUBA-itraconazole was 120% of the reference dose. Therefore, in the fasted state, SUBA-itraconazole was closer in exposure to the reference dose. The variability in exposure was less for SUBA-itraconazole (CV% of ~ 41%) than Sporanox (CV% of ~63%). This equates to an approximate 35% reduction in exposure variability for SUBA-itraconazole compared to Sporanox.

A similar difference is evident in **Table 9** when exposure is assessed by C_{max}. The median ICZ Cmax was 121 and 127% of the reference dose for the fed and fasted state, respectively. Therefore, in the fed state, SUBA-itraconazole was closer in exposure to the reference dose.

Multi-Dose Administration:

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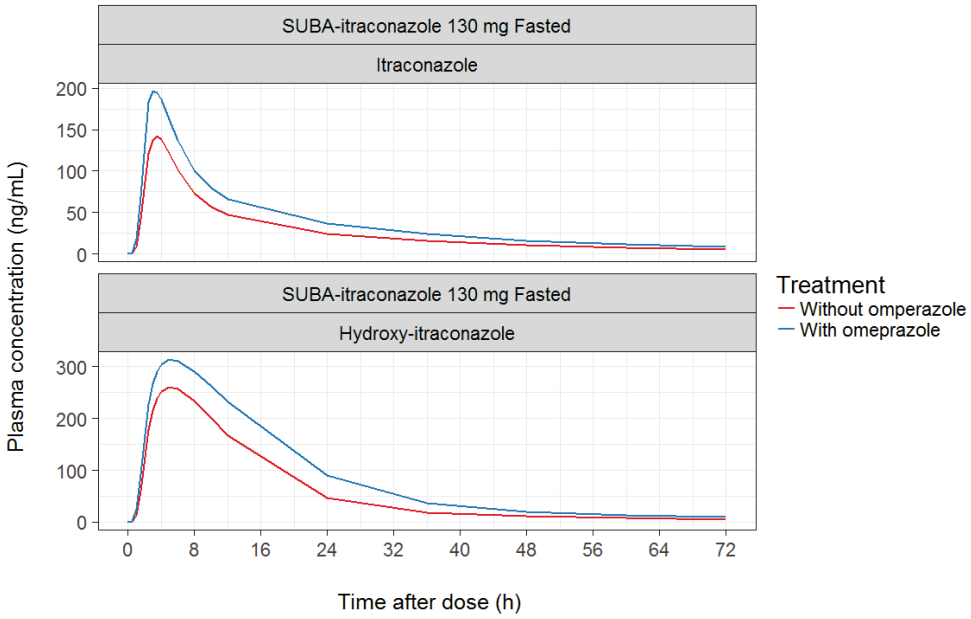
Table 10 and **Figure 2** show a summary of ICZ and HICZ exposure for Sporanox and SUBA-itraconazole in the fed state and multi-dose setting. The pattern of differences observed for the single-dose setting was similar, with concentrations for 65 mg SUBA-itraconazole capsule above the reference. However, the differences between the formulations were larger in the multi-dose setting due to the impact of the higher concentrations on non-linear metabolism of the drug. The median AUC0-72 was 153% and 131% of the reference after once and twice daily administration of two capsules (2×65 mg), respectively. A similar pattern was evident when exposure was assessed by Cmax. The distribution of Tmax did not differ noticeably between the two formulations.

Omeprazole Effects: The effect of omeprazole on the model predicted ICZ and HICZ concentrations is shown in

Figure 11. The population effect of concomitant omeprazole administration with SUBA-itraconazole was to increase the AUCinf and AUC0-72 of ICZ to 142-150%, to increase Cmax to 133-139% of that of SUBA-itraconazole without omeprazole co-administration. The Tmax stayed almost the same (97-100%) between the two treatment periods. The omeprazole effects on ICZ exposure resulted in a corresponding effect on HICZ exposure. The population effect of concomitant omeprazole administration with SUBA-itraconazole was to increase the AUCinf and AUC0-72 of HICZ to 140-150%, to increase Cmax to 117-122% of that of SUBA-itraconazole without omeprazole co-administration.

Figure 11 : Predicted Omeprazole Effect on Median Itraconazole and Hydroxy-itraconazole Concentrations



Model median predicted ICZ and HICZ concentrations for 130 mg SUBA-itraconazole based on 1000 simulated subjects per dose

Source: Figure 56 on page 111 of sponsor's population PK report

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Reviewer's Comments: The sponsor's population PK analyses are acceptable. The goodness-of-fits plots show that the final model can adequately describe the observed concentration of itraconazole and hyroxy-itraconaozle in both SUBA-itraconazole and Sporanox formulations. The PK parameter estimates are reasonable. The final model was able to describe the effect of food, omeprazole, and formulation. The predictive performance of the final model for different formulations and doses as demonstrated by the VPC plots is good. Independent analysis by the FDA reviewer was conducted and the results were consistent with those of the Applicant.

(b) (4)

SUBA 65 mg is the dose that will be included in the label.

Reviewer's Analysis

Introduction

The Division of Pharmacometrics has reviewed the modeling and simulation analyses provided in this submission. The review team identified that SUBA-itraconazole and Sporanox is not bioequivalent. Multiple-dose of SUBA 65 mg b.i.d under fed state can result in AUC ratio of SUBA/Sporanox to be 169% and and C_{max} ratio of SUBA/Sporanox to be 153%. Safety of SUBA is then a potential concern for the review team. An exposure-response relationship for AEs were conducted by the pharmacometric reviewer, however, there was no clear relationship revealed. Safety data for SUBA 65 mg in patients are not available.

Objectives

Independent analyses were conducted by FDA pharmacometric reviewers to available exposure data to conduct an exposure-response analysis for safety.

Methods

Data Sets: The datasets used by the reviewer were submitted by the Applicant. AE and Exposure data were from multiple dose studies MPG012, MPG015, and MPG017.

Software: SAS for windows 9.3 was used for all graphing and statistical analyses.

Results: Exposure-response Relationship for safety

Independent analysis of the exposure-response relationship for safety in adult healthy subjects was conducted by the reviewer using data from multiple dose studies (MPG012, MPG015, MPG017). A logistic regression analysis was applied to see the overall trend of change between itraconazole C_{max} and proportions of subjects experiencing at least one AE while taking SUBA-itraconazole 65 mg Capsules. Similar to results submitted by the Applicant, there was no clear relationship between itraconazole and AEs (**Figure 12**). Higher itraconazole exposure was not associated with higher proportions of subjects with at least one AE.

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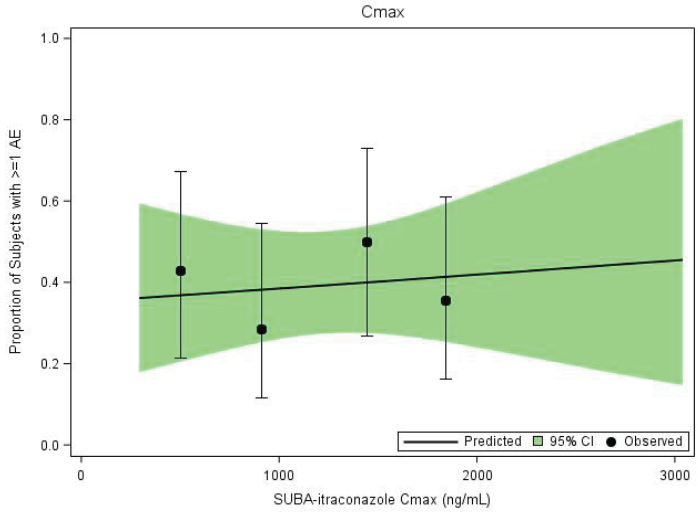
Figure 12: Relationship between Itraconazole Exposure and Probability of AE



In summary, the exposure of itraconaozle in SUBA is estimated to be slightly higher than in Sporanox. However, SUBA demonstrate less variability in Cmax and AUC compared to Sporanox, the maximum C_{max} from SUBA is still within the range observed with Sporanox. If the exposure-response relationship for safety is the same between healthy subjects and patients, the higher exposures from SUBA are not expected to result in an increase in serious safety events. Under fed status, the exposure is comparable between these two products. Therefore, SUBA 65 mg is recommended to be administered with food to avoid undesired high concentrations.

16 Division Director (Clinical)

Concur with review.

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/s/

ALISON K RODGERS
12/10/2018

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