NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	214900
Priority or Standard	Priority
Submit Date	October 01, 2020
Received Date	October 01, 2020
PDUFA Goal Date	June 01, 2021
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	June 1, 2021
Established/Proper Name	Ibrexafungerp
(Proposed) Trade Name	BREXAFEMME
Pharmacologic Class	Triterpenoid antifungal
Code names	SCY-078, MK-3118
Applicant	SCYNEXIS, Inc.
Dosage form	Tablet
Applicant proposed Dosing Regimen	300 mg (two tablets of 150 mg) twice a day for one day
Applicant Proposed Indication/Population	Treatment (b) (4) adult women with vulvovaginal candidiasis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	72605008 Candidal vulvovaginitis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC)
Recommended SNOMED CT Indication Disease Term for each Indication	72605008 Candidal vulvovaginitis (disorder)
Recommended Dosing Regimen	300 mg (two tablets of 150 mg) administered approximately 12 hours apart for one day; with concomitant use of a strong CYP3A inhibitor, adjust dose to 150 mg (one of the 150 mg tablet) administered approximately 12 hours apart for one day

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jacquelyn Rosenberger, PharmD, RAC
Chief, Regulatory Project Management Staff	Maureen Dillon-Parker, MS, RAC
Nonclinical Reviewer	James S. Wild, PhD
Nonclinical Team Leader	Terry Miller, PhD
Office of Clinical Pharmacology Reviewer(s)	Cristina Miglis, PharmD, MS, BCPS
Office of Clinical Pharmacology Team Leader(s)	Zhixia (Grace) Yan Danielsen, PhD
Clinical Reviewer	Heidi Smith, MD, PhD
Clinical Team Leader	Thomas Smith, MD
Statistical Reviewer	Cheryl Dixon, PhD
Acting Associate Division Director (OB/DBIV)	Karen Higgins, ScD
Clinical Microbiology Reviewer	Simone Shurland, PhD
Clinical Microbiology Team Leader	Avery Goodwin, PhD
Cross-Disciplinary Team Leader	Thomas Smith, MD
Division Director (DPT-ID)	Hanan Ghantous, PhD, DABT
Division Director (OCP)	Kellie Reynolds, PharmD
Division Director (DAI)	Sumathi Nambiar, MD, MPH
Office Deputy Director (OID)	Adam Sherwat, MD

Additional Reviewers of Application

OPQ	Dorota Matecka, PhD (Application Technical Lead)
DPMH	Niquiche Guity, PhD/Tamara Johnson, MD, MS
OPDP	Carrie Newcomer, PharmD/James Dvorsky, PharmD
OSI	Cheryl Grandinetti, PharmD/Phillip Kronstein, MD
OSE/DEPI	Monisha Billings, DDS, MPH, PhD/Natasha Chih-Ying Chen, PhD
OSE/DMEPA	Deborah Myers RPh, MBA/Valerie Vaughn, PharmD
OSE/DRM	Mei-Yean Chen, PharmD, BCOP/Naomi Boston, PharmD
OSE/DPV	Rachna Kapoor, PharmD

DBIV=Division of Biometrics IV
OB=Office of Biostatistics
DPT-ID=Division of Pharmacology/Toxicology – Infectious Diseases
OCP=Office of Clinical Pharmacology
DAI=Division of Anti-Infectives
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Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	James Wild, PhD	OID/DPTID	Sections: 4.2, 5	Select one: ___x Authored ___ Approved
	Signature: James Wild -S Digitally signed by James Wild -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=James Wild -S, 0.9.2342.19200300.100.1.1=2000340798 Date: 2021.06.01 11:11:30 -04'00'			
Nonclinical Supervisor	Terry Miller, PhD	OID/DPTID	Sections: 4.2, 5	Select one: ___ Authored ___x Approved
	Signature: Terry J. Miller -S Digitally signed by Terry J. Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S Date: 2021.06.01 11:01:52 -04'00'			
Nonclinical Division Director	Hanan Ghantous, PhD, DABT	OID/DPTID	Sections: 4.2, 5	Select one: ___ Authored ___x Approved
	Signature: Terry J. Miller -S Digitally signed by Terry J. Miller -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300233444, cn=Terry J. Miller -S Date: 2021.06.01 13:31:28 -04'00'			
Clinical Pharmacology Reviewer	Cristina Miglis, PharmD, MS, BCPS	OCP/DIDP	Sections: 6, 11, 16.4.1, 16.4.2	Select one: __x_ Authored ___ Approved
	Signature: Cristina M. Miglis -S Digitally signed by Cristina M. Miglis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002342670, cn=Cristina M. Miglis -S Date: 2021.06.01 13:55:57 -04'00'			
Product Quality Team Leader	Dorota Matecka, PhD	OPQ	Sections: 4.2	Select one: __x_ Authored ___ Approved
	Signature: Dorota M. Matecka -S Digitally signed by Dorota M. Matecka -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S Date: 2021.06.01 10:29:29 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Zhixia (Grace) Yan Danielsen, PhD	OCP/DIDP	Sections: 6, 11, 16.4.1, 16.4.2	Select one: ___ Authored __x_ Approved
	Signature: Zhixia Y. Danielsen -S Digitally signed by Zhixia Y Danielsen -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2000794117 cn=Zhixia Y Danielsen -S Date: 2021 06 01 09:52:20 04'00'			
Pharmacometrics Reviewer	Hezhen Wang, PhD	OCP/DIDP	Section: 16.4.3	Select one: _x__ Authored ___ Approved
	Signature: Hezhen Wang -S (Affiliate) Digitally signed by Hezhen Wang -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002094069, cn=Hezhen Wang -S (Affiliate) Date: 2021.06.01 12:44:00 -04'00'			
Pharmacometrics Team Leader	Justin Earp, PhD	OCP/DIDP	Section: 16.4.3	Select one: ___ Authored __x_ Approved
	Signature: Hezhen Wang -S (Affiliate) Digitally signed by Hezhen Wang -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002094069, cn=Hezhen Wang -S (Affiliate) Date: 2021.06.01 12:45:19 -04'00'			
Division Director (OCP)	Kellie Reynolds, PharmD	OCP/DIDP	Sections: 6, 11, 16.4	Select one: ___ Authored __x_ Approved
	Signature: Kellie S. Reynolds -S Digitally signed by Kellie S. Reynolds -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300093770, cn=Kellie S. Reynolds -S Date: 2021.06.01 09:44:28 -04'00'			
Clinical Reviewer	Heidi Smith, MD, PhD	OID/DAI	Sections: 1-3, 4.1, 8.2, 8.4, 9-13, 19.2, 19.7	Select one: __x_ Authored ___ Approved
	Signature: Heidi L. Smith -S Digitally signed by Heidi L. Smith -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Heidi L. Smith -S, 0.9.2342.19200300.100.1.1=2002524995 Date: 2021.06.01 10:04:45 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Thomas Smith, MD	OID/DAI	Sections: 1-3, 4.1, 8.2, 8.4, 9-13, 19.2, 19.7	**Select one:** ___ Authored __x_ Approved
	Signature: Thomas D. Smith -S Digitally signed by Thomas D. Smith -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300154381, cn=Thomas D. Smith -S Date: 2021.06.01 12:58:47 -04'00'			
Clinical Microbiology Reviewer	Simone Shurland, PhD	OID/DAI	Sections: 4.3, 16.3	**Select one:** __X_ Authored ___ Approved
	Signature: Simone Shurland -S Digitally signed by Simone Shurland -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000273852, cn=Simone Shurland -S Date: 2021.06.01 12:31:28 -04'00'			
Clinical Microbiology Team Leader	Avery Goodwin, PhD	OID/DAI	Sections: 4.3, 16.3	**Select one:** ___ Authored _X__ Approved
	Signature: Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300211785, cn=Avery C. Goodwin -S Date: 2021.06.01 09:59:18 -04'00'			
Statistical Reviewer	Cheryl Dixon, PhD	OB/DBIV	Sections: 8.1, 8.3	**Select one:** __X_ Authored ___ Approved
	Signature: Cheryl A. Dixon -S Digitally signed by Cheryl A. Dixon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300115195, cn=Cheryl A. Dixon -S Date: 2021.06.01 11:22:44 -04'00'			
Acting Associate Division Director (OB)	Karen Higgins, ScD	OB/DBIV	Sections: 8.1, 8.3	**Select one:** ___ Authored ___X Approved
	Signature: Karen M. Higgins -S Digitally signed by Karen M. Higgins -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300117310, cn=Karen M. Higgins -S Date: 2021.06.01 11:44:00 -04'00'			
Regulatory Project Manager	Jacquelyn Rosenberger, PharmD, RAC	ORO/DRO-ID/AI2	Section 3:	**Select one:** ___ Authored _X_ Approved
	Signature: Jacquelyn C. Rosenberger -S Digitally signed by Jacquelyn C. Rosenberger -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001600857, cn=Jacquelyn C. Rosenberger -S Date: 2021.06.01 13:59:44 -04'00'			

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Chief, Regulatory Project Management Staff	Maureen Dillon-Parker, MS, RAC	ORO/DRO-ID/AI2	Section 3:	**Select one:** ___ Authored _X_ Approved
	Signature: Maureen P. Dillon Parker -S Digitally signed by Maureen P. Dillon Parker -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042254, cn=Maureen P. Dillon Parker -S Date: 2021.06.01 10:17:56 -04'00'			
Division Director (Clinical)	Sumathi Nambiar, MD, MPH	OID/DAI	Sections: 14	**Select one:** _X__ Authored ___ Approved
	Signature: See signature in DARRTS			
Associate Director for Labeling	Abimbola Adebowale, PhD	OID/DAI	Sections: 11	**Select one:** _ _ Authored __X_ Approved
	Signature: Abimbola O. Adebowale -S Digitally signed by Abimbola O. Adebowale -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300141826, cn=Abimbola O. Adebowale -S Date: 2021.06.01 10:46:11 -04'00'			
Office Deputy Director	Adam Sherwat, MD	OID	Sections: 15	**Select one:** _X__ Authored ___ Approved
	Signature: See signature in DARRTS			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BID	twice daily
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
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
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
DVT	deep vein thrombosis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
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
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PE	pulmonary emboli
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RRA	remote regulatory audit
REMS	risk evaluation and mitigation strategy
RHD	recommended human dose
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SMQ	standardized MedDRA query
SOC	standard of care
TAT	thrombin-antithrombin
TEAE	treatment emergent adverse event
VSS	vulvovaginal signs and symptoms
VVC	vulvovaginal candidiasis

1 Executive Summary

1.1. Product Introduction

Oral ibrexafungerp (Brexafemme) is a triterpenoid antifungal drug that inhibits glucan synthase, an enzyme involved in formation of the 1,3-β-D-glycan component of the fungal cell wall. In this NDA, the Applicant is seeking the indication for the treatment of vulvovaginal candidiasis (VVC) in (b) (4) adult women. The proposed dosing regimen is two 300 mg doses administered orally approximately 12 hours apart. With concomitant use of a strong CYP3A inhibitor, the dosing is modified to two 150 mg doses administered orally approximately 12 hours apart.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of the effectiveness and sufficient safety information to support approval of oral ibrexafungerp for the treatment of VVC in post-menarchal females. Two randomized, placebo-controlled trials in adults with VVC demonstrated a clinically meaningful improvement in outcomes and statistical superiority of ibrexafungerp over placebo in clinical cure of VVC at Day 8-14 post-treatment. Data from these two trials along with supportive data from Phase 1 and 2 trials demonstrate the safety of oral ibrexafungerp 300 mg twice daily for 1 day for VVC treatment. The safety and effectiveness of oral ibrexafungerp for treatment of VVC in postmenarchal adolescents have been established based on data from adequate and well-controlled studies in adults and from summary safety data from a pharmacokinetic and safety study in adolescents. Since severe fetal malformations were observed in rabbit studies at exposures < 25-fold the human exposures at the maximum recommended human dose (MRHD) with an NOAEL at exposures < 10-fold the human exposure at the MRHD, VVC is a non-life-threatening infection, and other effective treatment options are available for VVC treatment, the label will state that oral ibrexafungerp is contraindicated in pregnant women.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 214900, the Applicant is seeking approval of oral ibrexafungerp (300 mg twice daily for 1 day) for the treatment of VVC in (b) (4) adult women. Oral ibrexafungerp is a triterpenoid antifungal drug that inhibits glucan synthase, an enzyme involved in formation of the 1,3-β-D-glycan component of the fungal cell wall.

VVC is characterized by vulvovaginal inflammation (itching, burning, irritation, edema, redness, excoriation) in the presence of yeast. VVC is a common condition, with 75% of women experiencing at least one episode. In the U.S., current VVC treatment options are azole antifungal drugs administered orally or intravaginally. While most VVC episodes are caused by *Candida albicans* and respond to azole antifungals (70-80% clinical cure), some non-albicans species such as *C. glabrata* have lower response rates.

Oral ibrexafungerp was evaluated in two randomized, placebo-controlled trials (VANISH-303 and VANISH-306) enrolling non-pregnant post-menarchal females with acute VVC. The primary endpoint of both trials was clinical cure (defined as complete resolution of VVC signs and symptoms on Day 11±3) in subjects who had yeast isolated from pre-treatment vaginal fluid samples and who had received at least one dose of study treatment. In the VANISH-303 trial conducted in the U.S., 50% of ibrexafungerp-treated subjects experienced clinical cure compared to 28% of placebo-treated subjects [treatment difference, 22%, 95% CI (10.2, 32.8), p=0.001]. In the VANISH-306 trial conducted in the U.S. and Bulgaria, 64% of ibrexafungerp-treated subjects experienced clinical cure compared to 45% of placebo-treated subjects [treatment difference, 19%, 95% CI (6.0, 30.6), p=0.009]. Only one adolescent was enrolled in the clinical trials and this patient was in the placebo arm; however, the similarity of the disease pathophysiology in postmenarchal adolescents and adult women allows extrapolation of efficacy for VVC treatment.

The safety database included 575 adults treated with oral ibrexafungerp 300 mg twice daily for one day in Phase 2 and Phase 3 trials, along with an additional 492 adults receiving different oral ibrexafungerp doses or treatment durations. The most frequent adverse reactions with oral ibrexafungerp were gastrointestinal disorders, most commonly diarrhea, nausea, and abdominal pain. Less common adverse reactions were elevated transaminases and hypersensitivity. While lower extremity deep vein thromboses and pulmonary emboli occurred in subjects enrolled in a trial of intravenously administered ibrexafungerp, no thrombotic events were observed in trials of oral ibrexafungerp and the ibrexafungerp dosing regimen proposed for VVC treatment is not anticipated to increase the risk of thrombosis. Based on findings of severe fetal malformations (including phocomelia and anencephaly) when oral ibrexafungerp was administered to pregnant rabbits, oral ibrexafungerp may pose a risk of fetal toxicity. Since ibrexafungerp is a substrate of CYP3A4, ibrexafungerp dose reduction is recommended with concomitant use of strong CYP3A inhibitors and use of ibrexafungerp with moderate and strong CYP3A inducers should be avoided. As the safety profile of oral ibrexafungerp in adolescents is not expected to be different from that of adults, the indication will include postmenarchal pediatric patients. Preliminary data from a recently completed oral ibrexafungerp pharmacokinetics and safety study in adolescent

females confirmed that similar adverse reactions were observed in this population. The final clinical study report will be submitted as a postmarketing commitment (PMC).

Based on the efficacy and safety data from two placebo-controlled Phase 3 trials of oral ibrexafungerp in adults with VVC and extrapolation of the data from these trials along with additional safety data in adolescents, the labeled indication is for the treatment of VVC in postmenarchal females. Clinical cure rates in patients with VVC receiving oral ibrexafungerp were significantly higher than in patients receiving placebo. While gastrointestinal adverse reactions were common with oral ibrexafungerp, these reactions were mostly mild and of short duration. Due to findings of severe fetal malformations in animal studies, oral ibrexafungerp is contraindicated in pregnancy. The Applicant will conduct a single-arm descriptive study of women incidentally exposed to oral ibrexafungerp during pregnancy and a milk-only lactation study in lactating women receiving therapeutic doses of oral ibrexafungerp as postmarketing requirements (PMRs). The overall benefit-risk profile of ibrexafungerp is favorable to support an indication for the treatment of postmenarchal females with VVC. In our decision to approve ibrexafungerp, we considered the available safety and efficacy data, and the recommendation for approval by all review disciplines.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Vulvovaginal candidiasis (VVC) is characterized by vulvovaginal inflammation (itching, burning, irritation, edema, redness, excoriation) in the presence of yeast. • VVC is mostly commonly caused by *Candida albicans*. • Complicated VVC is characterized by severe symptoms, isolation of yeast other than *C. albicans*, recurrent episodes, or occurrence in patients with diabetes or immunocompromising conditions. • 75% of women will experience ≥ 1 episode of VVC, 40-45% will experience multiple VVC episodes, and 10-20% will experience complicated VVC.	VVC is a common condition, with the majority of women experiencing at least 1 episode.
Current Treatment Options	• VVC treatments include oral and intravaginal antifungal drugs, available by prescription or over-the-counter. • Fluconazole, an azole antifungal drug, is the only approved oral VVC therapy. • In the U.S., the other currently available VVC treatments are intravaginal azole antifungals; intravaginal nystatin (a polyene antifungal) was approved, but it is no longer marketed in the U.S. • While most VVC cases respond to oral or intravaginal azole treatment (70-80% clinical cure), VVC caused by non-albicans species (such as *C. glabrata*) has lower response rates.	Currently available treatments for VVC are effective but rely upon a single class of antifungals (azoles). Azole antifungals have lower cure rates for VVC caused by non-albicans

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td></td><td>species of Candida.</td></tr>
<tr><td>Benefit</td><td>
• Oral ibrexafungerp was evaluated in two trials enrolling non-pregnant postmenarchal females with acute VVC randomized 2:1 to receive placebo or ibrexafungerp (300 mg twice daily x 1 day).
• The primary endpoint was clinical cure, defined as complete resolution of VVC signs and symptoms at Day 11±3, in patients who had Candida species cultured at baseline and received at least one dose of study treatment.
<table>
<tr><th></th><th colspan="3">Trial 1 (VANISH-303)</th><th colspan="3">Trial 2 (VANISH-306)</th></tr>
<tr><th></th><th>Ibrexafungerp (N=190)</th><th>Placebo (N=100)</th><th>Difference (95% CI) P-value</th><th>Ibrexafungerp (N=189)</th><th>Placebo (N=89)</th><th>Difference (95% CI) P-value</th></tr>
<tr><td>Clinical Cure (Day 11±3)</td><td>95 (50.0%)</td><td>28 (28.0%)</td><td>22% (10.2, 32.8) p=0.001</td><td>120 (63.5%)</td><td>40 (44.9%)</td><td>19% (6.0, 30.6) p=0.009</td></tr>
</table>
• The trials demonstrated that patients with VVC treated with ibrexafungerp had significantly higher rates of clinical cure than patients treated with placebo.
• The trials' strengths include the racial diversity of the study population and the primary endpoint requiring full resolution of clinical signs and symptoms of VVC.
• The trials' limitations include exclusion of patients with some risk factors for complicated VVC (such as uncontrolled diabetes or immune deficiency), limited number of VVC cases due to non-albicans species, and the lack of adolescents in the ibrexafungerp arm.
• Efficacy of oral ibrexafungerp for treatment of VVC in postmenarchal adolescents has been established based on extrapolation of data from studies in adults.
</td><td>Patients with VVC treated with oral ibrexafungerp were more likely to achieve clinical cure than patients treated with placebo.

Since no adolescents were treated with oral ibrexafungerp in the Phase 3 trials, efficacy was extrapolated from the data obtained in adults.</td></tr>
<tr><td>Risk and Risk Management</td><td>
• The safety database consists of 575 adults with VVC treated with oral ibrexafungerp 300 mg twice daily for 1 day in Phase 2 and Phase 3 trials, with supportive data from an additional 492 adults treated with other oral ibrexafungerp doses and treatment durations in Phase 1 and Phase 2 trials.
• The safety profile of oral ibrexafungerp in adolescents is not expected to differ from adults and preliminary data from a recently completed PK and safety study in adolescent females confirmed that similar adverse reactions were observed. Final data from the adolescent study will be submitted as a PMC.
• Oral ibrexafungerp is contraindicated in pregnancy based on findings of severe fetal malformations
</td><td>Gastrointestinal effects are the most common adverse reactions with oral ibrexafungerp.

The safety profile is expected to be similar in adolescents and adults.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(including phocomelia and anencephaly) in rabbit studies. • Gastrointestinal disorders, most commonly diarrhea, nausea, and abdominal pain, were the most frequent adverse reactions with oral ibrexafungerp. • Less common reactions with oral ibrexafungerp were elevated transaminases and hypersensitivity. • Deep vein thromboses and pulmonary emboli were observed in a clinical trial of intravenous ibrexafungerp, but no thrombotic events occurred in the clinical trials of oral ibrexafungerp. The ibrexafungerp dosing regimen proposed for VVC treatment is not anticipated to increase risk of thrombosis. • Ibrexafungerp is a substrate of CYP3A4; ibrexafungerp dose reduction is recommended with concomitant use of strong CYP3A inhibitors and use of ibrexafungerp with moderate and strong CYP3A inducers should be avoided.	Final data from an adolescent PK and safety study will be submitted as a PMC. Due to severe fetal malformations in rabbit studies, oral ibrexafungerp is contraindicated in pregnancy. A single-arm study in women incidentally exposed to oral ibrexafungerp during pregnancy and a milk-only lactation study of oral ibrexafungerp in lactating women will be evaluated as PMRs. Use of ibrexafungerp with strong inhibitors of CYP3A requires dose reduction; use with moderate and strong CYP3A inducers should be avoided.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		Section 8.1.1, clinical outcome assessment (vulvovaginal signs and symptoms score) used in primary efficacy endpoint
		x	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

VVC is a syndrome defined by signs and symptoms of vulvovaginal inflammation in the presence of yeast. It is characterized by symptoms of pruritus, vaginal soreness, dyspareunia, dysuria, and abnormal vaginal discharge. Clinical signs include vulvar edema, fissures, excoriations, and thick vaginal discharge. An estimated 75% of women will experience at least one episode of VVC, 40-45% will experience multiple VVC episodes, and 10-20% will experience complicated VVC requiring additional diagnostic or therapeutic considerations.[1] VVC primarily occurs in adolescents and pre-menopausal women; VVC is rare in pre-pubertal girls.[2]

VVC is most commonly caused by *Candida albicans*. The incidence of non-albicans species as a cause of VVC varies by location (higher incidence in some areas of Asia and Africa) and patient population (higher incidence in diabetic women and HIV-infected women). *C. glabrata* is the most commonly isolated non-albicans species in VVC.[3]

VVC is classified as uncomplicated when it occurs in immunocompetent women, is likely to be caused by *C. albicans*, is characterized by mild to moderate symptoms, and is sporadic or infrequent. Complicated VVC is characterized by severe symptoms, isolation of non-albicans species, recurrent episodes, or occurrence in women with diabetes, immunocompromising conditions, debilitation, or immunosuppressive therapy.[4]

Diagnosis of VVC is made by identification of clinical signs and symptoms of vaginitis in combination with evidence of vaginal yeast by culture or microscopy [Gram stain or wet preparation with saline or potassium hydroxide (KOH)]. VVC is associated with a normal vaginal pH (<4.5). Since 10-20% of women have asymptomatic vaginal yeast colonization, identification of yeast without VVC signs or symptoms is not an indication for treatment.[5]

The FDA guidance document *Vulvovaginal Candidiasis: Developing Drugs for Treatment*[6] recommends the following eligibility criteria for trials evaluating drugs for postmenarchal females with VVC:

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[1] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[2] Achkar, J. M. and B. C. Fries (2010). "Candida Infections of the Genitourinary Tract." Clinical Microbiology Reviews **23**(2): 253-273.
[3] Ibid.
[4] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[5] Ibid.
[6] Food and Drug Administration (August 2019). Vulvovaginal Candidiasis: Developing Drugs for Treatment [Guidance for Industry].

- Two or more signs/symptoms of VVC (recommended ≥2 with at least moderate severity): itching, burning, irritation, edema, redness, excoriation
- KOH or saline preparation from inflamed mucosa or secretions demonstrating yeast forms (hyphae or pseudohyphae) or budding yeast
- Vaginal pH ≤4.5

Exclusion of patients with other infectious causes of vulvovaginitis, mixed infections, and those receiving VVC treatment within 14 days of enrollment

2.2. Analysis of Current Treatment Options

Approved treatments for acute VVC include prescription oral and intravaginal drugs and over-the-counter intravaginal drugs (**Table 1**). The triazole antifungal drug fluconazole, administered as a single 150 mg dose, is the only approved oral drug for VVC treatment. The intravaginal drugs currently available for acute VVC treatment in the U.S. are also azole antifungals and have similar efficacies to the oral fluconazole regimen.[7] While the choice of oral or intravaginal azole for acute VVC treatment is primarily a matter of patient preference,[8] the oral fluconazole labeling notes that the higher rates of adverse reactions observed in clinical trials (26% for oral fluconazole compared to 16% with intravaginal azole comparators) should be taken into consideration when selecting therapy.[9]

For treatment of uncomplicated VVC, some of the intravaginal drugs are available as higher concentration formulations that can be used in shorter regimens (1-3 days).[10] For complicated VVC, the Infectious Disease Society of America (IDSA) treatment guidelines recommend longer courses of intravaginal drugs (5-7 days) or oral fluconazole (150 mg every 72 h for 3 doses; not an approved dose for the VVC treatment indication).[11]

Infections with *C. glabrata* are less likely to be successfully treated with azole therapy. The IDSA guidelines include alternative treatment recommendations for *C. glabrata* VVC unresponsive to azole therapies, while acknowledging the low quality of the available evidence. These alternative treatments include intravaginal nystatin (FDA approved but not currently marketed in the U.S.), intravaginal boric acid (unapproved, must be compounded in capsules for intravaginal use), and flucytosine cream alone or in combination with topical amphotericin B (unapproved, must be compounded in a gel for intravaginal use).[12]

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[7] Pappas, P. G., et al. (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases **62**(4): e1-e50.
[8] Sobel, J. D. (2014). "Factors involved in patient choice of oral or vaginal treatment for vulvovaginal candidiasis." Patient Preference and Adherence **8**: 31-34.
[9] Diflucan (fluconazole tablets) [package insert]. New York, NY: Pfizer; 9/2020.
[10] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[11] Pappas, P. G., et al. (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases **62**(4): e1-e50.
[12] Ibid.

In patients with recurrent VVC, individual episodes caused by *C. albicans* generally respond to treatment for uncomplicated acute VVC.[13] There are no currently approved therapies for prevention of recurrent VVC. The IDSA treatment guidelines recommend an initial induction phase with 10-14 days of oral or intravaginal azole therapy followed by a maintenance azole regimen for 6 months (oral fluconazole 150 mg weekly or intravaginal clotrimazole once or twice weekly).[14]

While the IDSA treatment guidelines do not address treatment of VVC in pregnant women, CDC guidelines recommend only using 7-day intravaginal azole therapies for treatment of VVC during pregnancy.[15] Oral fluconazole labeling contains a warning for potential fetal harm, based on case reports describing a distinct pattern of congenital abnormalities in infants exposed to fluconazole during the first trimester or exposed to higher doses of fluconazole (400-800 mg/day). Retrospective epidemiologic studies have also identified a possible risk for congenital abnormalities or spontaneous abortion associated with lower dose fluconazole (150 mg as single or repeated doses) during the first trimester.[16]

Table 2-1 Summary of Treatments for Vulvovaginal Candidiasis

Product Name	Drug Class	Dosing/ Administration	Comments and Treatment Guidelines[17]
Prescription Drugs: Oral Administration			
Fluconazole oral tablets	Azole antifungal	150 mg tablet x 1 dose	• Clinical cure in VVC (2 trials):[18] - Oral fluconazole 239/347 (69%) - Intravaginal clotrimazole/miconazole 235/327 (72%) • IDSA treatment guidelines off-label use for: - Severe VVC: Fluconazole 150mg every 72 h x 2-3 doses - Recurrent VVC: Topical azole or oral fluconazole x 10-14 d then oral fluconazole 150 mg once weekly x 6 months
Prescription Drugs: Intravaginal Administration			
Butoconazole nitrate vaginal cream (2%)	Azole antifungal	5 g 2% cream x 1 dose	• Clinical cure in VVC (2 trials):[19] - Intravaginal butoconazole 95/118 (81%) - Intravaginal clotrimazole 93/116 (80%)
		5 g 0.4% cream daily x 7 d	• Clinical cure in VVC (1 trial):[20]

[13] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[14] Pappas, P. G., et al. (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases **62**(4): e1-e50.
[15] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[16] Diflucan (fluconazole tablets) [package insert]. New York, NY: Pfizer; 9/2020.
[17] Pappas, P. G., et al. (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases **62**(4): e1-e50.
[18] Diflucan (fluconazole tablets) [package insert]. New York, NY: Pfizer; 9/2020.
[19] Gynazole 1 (butoconazole nitrate cream) [package insert]. Allegan, MI: Perrigo; 11/2018.
[20] Terconazole vaginal cream, 0.8% [package insert]. Melville, NY: E. Fougera and Company; 12/2010.

Terconazole vaginal cream or suppositories	Azole antifungal	5 g 0.8% cream daily x 3 d 80 mg suppository daily x 3 d	- Intravaginal 0.8% terconazole 111/140 (79%) - Active control [different terconazole formulation] 101/153 (66%)
Nystatin vaginal suppository	Polyene antifungal	100, 000 units suppository daily x 14 d	• Topical azoles more effective than topical nystatin[21] • IDSA treatment guidelines alternative for VVC caused by *C. glabrata* • U.S. sales of nystatin suppository discontinued
Over-the-counter Drugs (Intravaginal Administration Only)			
Miconazole vaginal cream or suppositories	Azole antifungal	5 g 2% cream daily x 7 d 5 g 4% cream daily x 3 d 100 mg suppository daily x 7 d 200 mg suppository daily x 3 d 1200 mg suppository x 1 dose	• All topical azoles have similar efficacy; preparations available by prescription are not superior[22]
Clotrimazole vaginal cream	Azole antifungal	5 g 1% cream daily x 7 d 5 g 2% cream daily x 3 d	• IDSA treatment guidelines off-label use for recurrent VVC if oral fluconazole not feasible: - Clotrimazole vaginal cream 200 mg twice weekly *or* - Clotrimazole vaginal suppository 500 mg weekly • U.S. sales of clotrimazole suppository discontinued
Tioconazole vaginal ointment	Azole antifungal	5 g 6.5% ointment x 1 dose	
Unapproved Drugs (Intravaginal Administration Only)			
Boric acid intravaginal capsules		600 mg gelatin capsule daily x 14 d	• IDSA treatment guidelines alternative for *C. glabrata* unresponsive to oral azoles • Must be compounded
Flucytosine (17%) ± amphotericin (3%) vaginal gel	Nucleoside analog ± polyene antifungals	1000 mg flucytosine ±100 mg amphotericin B daily x 14 d	• IDSA treatment guidelines alternative for *C. glabrata* unresponsive to oral azoles • Must be compounded

Source: Clinical reviewer

[21] Centers for Disease Control and Prevention (2015). "Sexually Transmitted Diseases Treatment Guidelines, 2015." MMWR Recomm Rep **64**((No. RR-3)): 1-137.
[22] Pappas, P. G., et al. (2015). "Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America." Clinical Infectious Diseases **62**(4): e1-e50.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ibrexafungerp is a new molecular entity (NME) and is not approved in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Scynexis, Inc. submitted NDA 214900 (ibrexafungerp tablet 150 mg for treatment of VVC) on 01 October 2020. Ibrexafungerp was previously known as SCY-078 and MK-3118. It was studied under two IND applications:

- IND 107521 for oral ibrexafungerp was filed on 12 January 2010 by Merck and Co., Inc. IND ownership was transferred to Scynexis, Inc. on 24 May 2013. All clinical studies to support the safety and efficacy of oral ibrexafungerp for VVC treatment were conducted under this IND, except the Phase 2 proof-of-concept VVC treatment trial (SCY-078-203) and the cardiac safety evaluation (SCY-078-106). Studies evaluating prevention of recurrent VVC and treatment of invasive fungal infections are ongoing.

- IND 120869 for intravenous (IV) ibrexafungerp was filed on 13 January 2014 by Scynexis, Inc. One study submitted to NDA 214900 was conducted under this IND (SCY-078-106). On 28 February 2017, IND 120869 was placed on clinical hold due to development of thrombotic events in a multiple ascending dose study (SCY-078-109). The Sponsor did not submit a complete response prior to requesting IND inactivation on 18 April 2018.

Key regulatory interactions during oral ibrexafungerp development are summarized below:

- (b) (4)

- On 17 September 2013, a second EOP1 meeting was held with the new Sponsor (Scynexis) to discuss plans for redesigned Phase 2 development for treatment of invasive candidiasis. Discussion focused on the planned study population, evaluation of multiple dose levels, and selection of endpoints.

- On 24 January 2014 and 18 December 2014, oral ibrexafungerp was granted Qualified Infectious Disease Product (QIDP) designation and Fast Track designation respectively, for treatment of invasive candidiasis (including candidemia) and invasive aspergillosis.

- On 02 June 2014, a Type B meeting was held to discuss additional plans for Phase 2 development for treatment of invasive candidiasis. Discussion focused on

(b) (4)

- On 28 February 2017, IND 120869 for IV ibrexafungerp was placed on full clinical hold following the development of deep vein thrombosis and/or pulmonary emboli in 3 healthy volunteers in a multiple ascending dose Phase 1 study (SCY-078-109).

(b) (4)

- On 21 June 2017, a Type B meeting was held to discuss plans for Phase 3 development of oral ibrexafungerp for treatment of acute VVC and prevention of recurrent VVC. Discussion focused on the nonclinical studies needed to support treatment durations (1-3 d for acute VVC and 1-3 doses/month for $\leq$ 6 months for recurrent VVC) and design of the initial treatment phase for recurrent VVC. Assessments of thrombotic risks of ibrexafungerp were noted to be ongoing.

(b) (4)

- On 18 April 2018, the Sponsor requested inactivation of IND 120869 for IV ibrexafungerp; the Division's acknowledgment was sent 30 May 2018.

- On 18 April 2018 and 19 April 2018, oral ibrexafungerp was granted Fast Track designation and QIDP designation, respectively, for treatment of VVC and recurrent VVC.

- On 21 September 2018, an End-of-Phase 2 (EOP2) meeting was held to discuss plans for an oral ibrexafungerp NDA for VVC treatment and a supplemental NDA for prevention of recurrent VVC. Discussion included plans for additional evaluation of food effects on bioavailability, proposal for a concentration-QT analysis based on the SCY-078-106 multiple ascending dose IV ibrexafungerp trial in lieu of a dedicated thorough QT study, design of two identical Phase 3 placebo-controlled trials of oral ibrexafungerp treatment for acute VVC in females $\geq$ 12 y, and the size of the planned safety database.

(b) (4)

- On 08 February 2019, the Sponsor submitted a Special Protocol Assessment (SPA) request for a placebo-controlled Phase 3 trial of oral ibrexafungerp for prevention of recurrent VVC at a dose of 300 mg BID x 1 day, repeated every 4 weeks for 6 months. On 25 March 2019, the Division issued an SPA-No Agreement letter. On 18 July 2019, a revised SPA with modified primary endpoint, continuation of safety follow-up after recurrence or rescue medication use, use of a more conservative placebo response rate for sample size calculations, and removal of a planned interim analysis was agreed upon.

- On 25 February 2019, the Applicant submitted the Agreed Initial Pediatric Study Plan (Agreed iPSP) for treatment of VVC and prevention of recurrent VVC in pediatric patients $\geq$ 12 y. The Agreed iPSP included plans to enroll adolescents $\geq$12 y in the Phase 3 trials and a partial waiver for girls <12 y.

- On 22 March 2019, a Type B Chemistry Manufacturing and Control (CMC) meeting was held on the quality development program to enable submission of an oral ibrexafungerp NDA for VVC treatment.

- On 16 July 2019, the Applicant requested advice on the clinical pharmacology program to support an NDA for VVC treatment. On 16 September 2019, written responses included agreement that a renal impairment study was not required for the acute VVC indication and recommendations to complete a full hepatic impairment study and an ADME study with a single labeled oral dose of ibrexafungerp.

- On 09 September 2019, the Division requested information on dose- and duration-dependent toxicities observed in a 26-week rat study (peripheral neuropathy, irritation and metaplasia of stomach mucosa, thrombocytosis and alveolar phospholipidosis). The toxicities were observed at exposures similar to those attained clinically with oral ibrexafungerp 750 mg BID x 2 d then 750 mg daily in SCY-078-111. This dosing was also used in an ongoing Phase 3 trial of invasive fungal diseases (SCY-078-301). The Sponsor maintained that the no-observed-effect level (NOAEL) in the rat study was 3-fold higher than the expected human exposure and the observed findings were unlikely to be drug-related. A preliminary summary of safety from 5 subjects in SCY-078-301 receiving oral ibrexafungerp 750 mg daily for 6-12 months showed gastrointestinal adverse events (AE) similar to prior clinical studies, no peripheral neuropathy, and no thrombocytosis.

- On 6 April 2020, the Applicant submitted an Amended Agreed iPSP requesting a deferral of completion of an adolescent PK study because only 1 adolescent was enrolled in the Phase 3 VVC trials. On 19 June 2020, the Division informed the Applicant that a dedicated PK study in this age group is not necessary, extrapolation of efficacy from the adult population is acceptable and decisions on whether to issue postmarketing requirements would be made during NDA review.

- On 25 June 2020, a pre-NDA CMC meeting was held. Discussion focused on the proposed control strategy for starting materials and key intermediates, steps to assure the stereospecific configuration of the drug product, proposed in vitro dissolution methods, and stability testing plans.

- On 26 June 2020, a pre-NDA meeting was held to discuss the content of an oral ibrexafungerp NDA for VVC treatment. The discussion focused on use of individual trial data for efficacy analyses, timing of late submissions for the final reports of the plasma-binding study and the 12-month stability data, and confirmation that an adolescent PK study would not be required for NDA submission.

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

4.1. Office of Scientific Investigations (OSI)

The pivotal studies supporting the NDA were SCY-078-303 (VANISH-303) and SCY-078-306 (VANISH-306). SCY-078-303 was conducted only in the U.S., and SCY-078-306 was conducted in the U.S. and Bulgaria. The Office of Scientific Investigations (OSI) conducted clinical site inspections for selected U.S. study sites. Due to travel restrictions related to the COVID-19 pandemic, OSI conducted remote regulatory audits (RRAs) of study data from selected Bulgarian study sites. The audits were conducted at the Applicant's offices in Jersey City, NJ.

Study sites were selected for OSI inspection or RRA primarily based on the numbers of enrolled subjects, site efficacy rates, protocol deviations, and prior inspectional history. Four U.S. sites were selected for the SCY-078-303 study and two U.S. sites and two Bulgarian sites were selected for the SCY-078-306 study. Primary efficacy endpoint source data (Vulvovaginal Signs and Symptoms score assessments) were verified against the Applicant's data; 3 discrepancies were noted that were unlikely to have an impact on the overall efficacy results. Certified copies of the fungal culture results were verified, and no discrepancies were noted.

Overall, the pivotal studies appear to have been conducted adequately and the data generated appear acceptable to support the indication sought in the application.

4.2. Product Quality

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, ibrexafungerp tablets. The manufacturing and testing facilities have been found acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on February 25, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) – refer to the review dated April 14, 2021, in DARRTS.

Comments on Novel Excipients

Each of the excipients in the ibrexafungerp drug product have been used in higher amounts in previously approved oral drug products.

Table 4-1: The Amounts of Each Excipient in a 150 mg Ibrexafungerp Tablet and the Daily Dose of Ibrexafungerp.

Component	Quantity per 150 mg tablet	Quantity per daily 600 mg dose
Core Tablet		
Ibrexafungerp Citrate	189.49	757.96

(b) (4) microcrystalline cellulose (b) (4)	(b) (4)
Mannitol	
Crospovidone	
Colloidal Silicon Dioxide	
Magnesium Stearate	
Butylated Hydroxyanisole (BHA)	
Film Coat	
(b) (4)	(b) (4)
Hydroxypropylmethyl cellulose 2910 (Hypromellose 2910)	
Hydroxypropyl cellulose	
Titanium dioxide	
Talc	
FD&C Red #40	
FD&C Blue #2	

Comments on Impurities/Degradants of Concern

Drug Substance
There are no drug substance impurities of concern. The specified impurities that exceed the ICH qualification limits have been adequately qualified in the 13-week toxicology study in dogs (Table 4-2).

Table 4-2: Qualification of all the Specified Impurities in the Ibrexafungerp Drug Substance.

Impurity	Percent Impurity in Batch # 016CCB095	Impurity NOAEL[a] (mg/kg/day)	Impurity HED (mg/kg/day)[b]	Qualified % Impurity in 600 mg/day (10 mg/kg/day) dose of Ibrexafungerp[c]	Impurity Specifications for the Ibrexafungerp Drug Substance
(b) (4)					

(b) (4)

[a] The impurity NOAEL is equal to the percent of each impurity in Batch # 016CCB095 times the NOAEL for ibrexafungerp (60 mg/kg/day) in the 13-week toxicology study in dogs (Study No.: SCY078-TOX-012). The ibrexafungerp batch used in Study No.: SCY078-TOX-012 was Batch # 016CCB095.

[b] The impurity human equivalent dose (HED) is calculated by dividing the impurity NOAEL by a conversion factor of (b) (4) for dogs.

[c] The daily clinical dose of ibrexafungerp is 600 mg (10 mg/kg for a typical 60 kg human). The qualified percent of impurity is the impurity HED divided by the daily clinical dose of 10 mg/kg ibrexafungerp.

Potential Genotoxic Impurities

All the impurities associated with the starting materials, intermediates and specified in the drug substance were assessed for potential mutagenic structural alerts using two *in silico* QSAR prediction methodologies, expert rule based (Model GT_EXPERT) and statistical-based (Model GT1_BMUT) as recommended in the ICH M7 Guidance. The sum of the risk assessments for the ibrexafungerp starting materials and intermediates and in the drug substance indicate that all impurities will be controlled at levels that are individually or in combination below the limit of (b) (4) There are no potential genotoxic impurities of concern.

Residual Solvents

The residual solvents used in the manufacture of the ibrexafungerp drug substance, (b) (4) are all specified at the limits listed in the ICH Q3C guidance. There are no residual solvents of concern.

Elemental Impurities

Available data demonstrate all elemental impurities in the drug substance are consistently controlled below (b) (4)% of their respective ICH Q3D limits based on a maximum daily dose of 2 grams for the drug product. There are no elemental impurities of concern.

Drug Product

No new process impurities were identified in the drug product beyond those already observed in the drug substance. The degradation products that were identified in the drug product only occurred under forced degradation conditions. Consistent with ICH Q6A, only impurities that are degradation products in ibrexafungerp tablet 150 mg are monitored. No degradation products are formed during manufacture of ibrexafungerp 150 mg tablets and all impurities derived from the drug substance are considered process impurities which are controlled by the drug substance specifications and therefore not monitored in the drug product.

4.3. Clinical Microbiology

Ibrexafungerp, a semi-synthetic triterpenoid derivative of the natural product enfumafungin binds to glucan synthase and inhibits the synthesis of β-(1,3)-D-glucan, a component of fungal cell walls. The 1,3- β-D-glucan synthase complex includes *Fksp* (an integral membrane protein that is critical for glucan synthase activity) and *Rho1p* (a regulatory protein). It resides in the fungal cell wall and enables the incorporation of monomeric glucose into the fungal cell membrane polymer, β -(1,3)-D-glucan. Ibrexafungerp is structurally distinct from other classes of glucan synthesis inhibitors, such as the echinocandins, which also inhibit 1,3- β-D-glucan synthase. Their different molecular structures provide them with some unique characteristics in terms of microbiological activity.

Ibrexafungerp demonstrated activity with MIC_{90} values ranging from 0.015 – 4 µg/mL against *C. albicans, C. dubliniensis, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. lusitaniae, C. guillermondii, C. orthopsilosis, C. pelliculosa, C. kefyr*, and *C. auris*. The ibrexafungerp MIC_{90} values were lowest against *C. albicans* (0.015 – 0.25 µg/mL) and highest against *C. krusei* (1 – 4 µg/mL), *C. guillermondii* (4 µg/mL), *C. orthopsilosis* (4 µg/mL), and *C. lusitaniae* (4 µg/mL) (for further information **See Appendix 18.3**). The emergence of spontaneous resistant mutants against *C. glabrata* isolates showed that approximately 17% of *C. glabrata* mutants harbored mutations in the hot spot (HS1) region of *fks1* or *fks2* genes with most mutations localized to amino acid F659 within the HS1 region of *fks2*, with ibrexafungerp MIC values ranging from 1.26 to 3.17 µg/mL. Similarly, the ibrexafungerp MICs against *C. glabrata* mutants with no *fks* mutations ranged from 0.4 – 8 µg/mL (Jimenez-Ortigosa, 2017). Cross-resistance studies against *Candida* isolates that harbored known mutations in the HS1 region of either *fks1* or *fks2* showed that isolates with phenotypic or clinical resistance to echinocandins had ibrexafungerp MICs ranging from 0.06 -8 µg/mL, depending on the isolate. Studies have shown that modifications in position 641 of the *fks1* HS1 region in *C. albicans* isolates or 655 position in *fks1* for *C. krusei* or 625 position for *C. glabrata* and F659 position in *fks2* had greater impact on ibrexafungerp MICs compared to echinocandins (Pfaller [2013]; Marcos-Zambrano [2017]). Against fluconazole-resistant *Candida* spp. isolates, the ibrexafungerp MICs ranged from 0.06 – 2 µg/mL.

Time kill studies showed that ibrexafungerp demonstrated concentration-dependent and time-dependent fungicidal activity (defined as >3 log_{10} reduction in CFU) against *Candida* spp. including wild-type *C. albicans* (4x - >16X), *C. krusei* (1x), *C. glabrata* (1x - 4x), *C. parapsilosis* (16x) and *C. tropicalis* (>16x), *C. auris* (1x) as well as echinocandin-resistant *C. glabrata* (4x) at 24 hours. Ibrexafungerp minor metabolites, SCY-PYR and SCY-TBU, showed similar activity to ibrexafungerp (MIC_{50} of 0.5, 0.5 and 0.25 µg/mL, respectively).

The combination of ibrexafungerp with echinocandins (caspofungin, micafungin and anidulafungin) showed no antagonism against *C. albicans* (ATCC 90028) as well as fluconazole-resistant *C. albicans* strains (MYA-2732). Similarly, no antagonism was observed between

ibrexafungerp and azoles (fluconazole, ketoconazole, itraconazole, voriconazole and posaconazole) against *C. parapsilosis* ATCC 90018 and *C. glabrata* ATCC 90030 strains.

Ibrexafungerp showed mixed results following multiple dosing regimens in murine models of intra-abdominal *Candida* infection, disseminated and invasive candidiasis caused by azole and echinocandin susceptible and non-susceptible strains. There was evidence of persistence of fungal organisms in neutropenic and non-neutropenic models of ibrexafungerp treatment. None of the studies appeared to completely clear the fungal load in challenged animals. A summary of the results are as follows:

- In murine models of disseminated candidiasis, the activity of ibrexafungerp following BID administration by oral gavage at doses up to 200 mg/kg for 4 to 7 day. The isolates tested included *C. albicans, C. glabrata,* and *C. tropicalis* including echinocandin resistant strains with ibrexafungerp MICs ranging from 0.03 to 0.5 µg/mL. Against wild type *C. albicans* strains, there was not a clear difference in activity against WT clinical isolates with regards to MIC, suggesting no direct correlation between MIC and reduction in fungal burden. Against *C. tropicalis* strains (MIC <0.03 - 0.5 µg/mL), treatment with ibrexafungerp at 25 mg/kg BID resulted in reduction in tissue burden in 3 of 4 strains (60 – 100% sterilization); however, one strain (MIC 0.5 µg/mL) did not completely clear the fungal burden.
- In neutropenic murine models of disseminated candidiasis, the activity of ibrexafungerp following BID administration by oral gavage was studied at doses ranging from 10 to 40 mg/kg for 7 days. In some studies, ibrexafungerp was administered using a loading dose with a higher first dose followed by lower subsequent doses (i.e., 20 mg/kg loading dose with subsequent 10 mg/kg doses BID). The isolates tested included *C. albicans, C. glabrata*, and *C. auris* and included both wild type and echinocandin resistant strains with ibrexafungerp MICs ranging from 0.016 to 1 µg/mL against wild-type isolates and 0.25 - 2 µg/mL against echinocandin-resistant strains. Reduction in kidney fungal burden showed a dose-response against wild type *C. albicans* strains but not for resistant isolates and at lower doses showed more activity. Ibrexafungerp did not show any activity against echinocandin-resistant strain containing mutations at *fks1* F6411 at any dose tested (10/5 to 20/10 mg/kg BID).
- In a mouse model of intra-abdominal *Candida* infection, oral ibrexafungerp significantly reduced liver fungal burden in CD-1 mice challenged with *C. albicans* at 15 mg/kg BID for 2 to 3 days (0.52 and 0.8 $\log_{10}$ CFU/g average burden reductions compared to control, respectively).
- In a guinea pig model of cutaneous *Candida* infection, oral ibrexafungerp significantly reduced clinical score and skin fungal burden in guinea pigs challenged with cutaneous *C. auris* at 10 mg/kg BID compared to control. Reduced efficacy was observed at higher dose levels (20 and 30 mg/kg BID).

Two identical Phase 3 pivotal clinical studies (SCY-078-303 and SCY-078-306) evaluated the efficacy and safety of ibrexafungerp in women with acute VVC. The Phase 3 study design and results are described elsewhere in the review (see **Section 8.1**). The mITT population included

all women who had a positive culture for at least one *Candida* spp. at baseline. The majority of women tested positive for *C. albicans* (92.0% SCY-078-303 and 88.6% SCY-078-306) followed by *C. glabrata* (7.7% SCY-078-303 and 10.3% SCY-078-306). Less than 2% of the population had other *Candida* spp. **Table 4-4** and **Table 4-5** provide the ibrexafungerp MIC values in SCY-078-303 and SCY-078-306, respectively.

- Against *C. albicans,* the ibrexafungerp MIC_{90} value was 0.12 µg/mL, with MICs ranging from ≤0.016 – 1 µg/mL. Both studies showed a higher percentage of women with mycological eradication at the test of cure (TOC) visit in the ibrexafungerp group compared to the placebo group.
- Against *C. glabrata*, the ibrexafungerp MIC_{90} value was 0.5 µg/mL with MICs ranging from 0.12 to 1 µg/mL. In SCY-078-303 trial, all women who tested positive continued to have persistence of *C. glabrata* isolates at TOC. Similarly, in the VANISH 306 trial, the majority of subjects (80%) had persistence of the fungal isolate in the ibrexafungerp treated group at the TOC visit.
- Against other *Candida* spp. isolated at baseline in both studies, the ibrexafungerp MICs ranged from 0.25 – 4 µg/mL. The majority of the isolates had ibrexafungerp MICs ≤ 1 µg/mL, with the exception that in the SCY-078-306 trial, there was one subject who had *C. lusitaniae* isolated with MICs 4 µg/mL at baseline; this patient was a clinical failure and the fungal isolate persisted at TOC. In the VANISH 303 study, *Saccharomyces* spp. was identified in one subject; the ibrexafungerp MIC was 0.5 µg/mL, and this isolate persisted at the TOC visit. No conclusions can be made about the efficacy of ibrexafungerp against other *Candida* isolates, since there were less than 10 isolates per group.
- The SCY-078-306 trial was conducted in Bulgaria and the United States. The ibrexafungerp MIC values of patients in the U.S. were similar to those of subjects in Bulgaria. The distribution of baseline *Candida* isolates was similar in subjects from the U.S. compared to subjects from Bulgaria. One notable exception was that *C. kefyr* isolates were only observed in subjects from Bulgaria. In addition, the incidence of co-infection with other *Candida* spp. was slightly higher in subjects from Bulgaria (13/170; 7.6%) compared to subjects from the U.S. (3/102; 2.9%).

Table 4-3. Baseline fungal organisms by treatment groups in SCY-078-303 and SCY-078-306 (mITT population)

	SCY-078-303		SCY-078-306		
Fungal Species at baseline	**Ibrexafungerp (N = 188) n (%)**	**Placebo (N = 98) n (%)**	**Ibrexafungerp (N = 188) n (%)**	**Placebo (N = 84) n (%)**	**TOTAL**
C. albicans	173 (92.0)	90 (91.8)	165 (87.8)	76 (90.5)	504 (90.3)
C. dubliniensis	2 (1.1)	0	0	1 (1.2)	3 (0.5)
C. glabrata	11 (5.9)	11 (11.2)	20 (10.6)	8 (9.5)	50 (9.0)
C. inconspicua	0	0	1 (0.5)	0	1 (0.2)
C. keyfr	0	0	3 (1.6)	1 (1.2)	4 (0.7)
C. krusei	0	1 (1.0)	2 (1.1)	0	3 (0.5)
C. lusitaniae	1 (0.5	1 (1.0)	1 (0.5	0	3 (0.5)
C. norvegenesis	0	0	1 (0.5)	0	1 (0.2)
C. parapsilosis	1 (0.5)	0	3 (1.6)	0	4 (0.7)
C. tropicalis	4 (2.1)	1 (1.0)	3 (1.6)	3 (3.6)	11 (2.0)
Saccharomyces spp.	1 (0.5)	0	0	0	1 (0.2)

Table 4-4. Clinical Cure and Mycological eradication response at TOC by baseline ibrexafungerp MIC - mITT population (SCY-078-303)

	C. albicans			*C. glabrata*			*C. tropicalis*			*C. dubliniensis*		
MIC (µg/mL)	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**
≤ 0.016	10	5 (50.0)	7 (70.0)	--	--	--	--	--	--	--	--	--
0.03	33	18 (54.5)	17 (51.5)	--	--	--	--	--	--	--	--	--
0.06	80	34 (42.5)	41 (51.2)	--	--	--	2	0 (0)	1 (50.0)	--	--	--
0.12	45	26 (57.8)	20 (44.4)	1	0 (0)	0 (0)	1	1 (100.0)	0 (0)	2	1 (50.0)	1 (50.0)
0.25	7	5 (71.4)	5 (71.4)	4	2 (50.0)	0 (0)	--	--	--	--	--	--
0.5	--	--	--	5	2 (20.0)	0 (0)	1	1 (100.0)	1 (100.0)	--	--	--
1	--	--	--	1	0 (0)	0 (0)	--	--	--	--	--	--
ALL SUBJECTS	**175**	**88 (50.3)**	**89 (51.4)**	**11**	**4 (36.4)**	**0 (0)**	**4**	**2 (50.0)**	**2 (50.0)**	**2**	**1 (50.0)**	**1 (50.0)**

Other Candida spp. were isolated in 1 subject each in the following :

- *C. lusitaniae* MIC 1 µg/mL – Clinical cure but mycological persistence
- *C. parapsilosis* MIC 0.12 µg/mL – Clinical cure and mycological eradication
- *Saccharomyces* spp. MIC 0.5 µg/mL – Clinical failure and mycological persistence

Source: **Microbiology Dataset**

Table 4-5. Clinical Cure and Mycological eradication response at TOC by baseline ibrexafungerp MIC - mITT population (SCY-078-306)

	C. albicans			*C. glabrata*			*C. keyfr*			*C. parapsilosis*			*C. tropicalis*		
MIC (µg/mL)	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**	**N**	**Clinical Cure**	**Mycological Eradication**
≤ 0.016	8	4 (50.0)	2 (25.0)	--	--	--	--	--	--	--	--	--	--	--	--
0.03	38	30 (78.9)	25 (65.8)	--	--	--	--	--	--	--	--	--	--	--	--
0.06	79	50 (63.3)	57 (72.1)	--	--	--	--	--	--	--	--	--	--	--	--
0.12	38	24 (63.2)	23 (60.5)	1	1 (100.0)	0 (0.0)	--	--	--	--	--	--	2	1 (50.0)	0 (0.0)
0.25	4	2 (50.0)	2 (50.0)	6	2 (33.3)	2 (33.3)	1	1 (100.0)	1 (100.0)	1	0 (0.0)	0 (0.0)	1	0 (0.0)	0 (0.0)
0.5	--	--	--	11	7 (63.6)	2 (18.2)	2	0 (0)	0 (0.0)	2	2 (100.0)	1 (50.0)	--	--	--
1	--	--	--	1	0 (0.)	0 (0.0)	--	--	--	--	--	--	--	--	--
ALL SUBJECTS	**165**	**107 (64.8)**	**107 (64.8)**	**20**	**11 (55.0)**	**4 (20.0)**	**3**	**1 (33.3)**	**1 (33.3)**	**3**	**2 (66.7)**	**1 (33.3)**	**3**	**1 (33.3)**	**0 (0)**

Two patients had *C. krusei* at baseline, one subject with ibrexafungerp MIC 0.5 µg/mL (Clinical cure, Mycological Persistence) and one subject with ibrexafungerp MIC 1 µg/mL (Clinical failure, Mycological Persistence).

Other Candida spp. were isolated in 1 subject each in the following

- *C. inconspicua* MIC 0.5 µg/mL – Clinical failure and mycological persistence
- *C. lusitaniae* MIC 4 µg/mL – Clinical failure and mycological persistence
- *C. norvegenesis* MIC 0.25 µg/mL – Clinical cure and mycological eradication

Source: **Microbiology Dataset**

Subjects treated with ibrexafungerp had isolates that were available at the TOC visit for comparison to baseline. Some of these subjects had mixed infections at baseline or TOC; however, only the *Candida* species observed at both time points were evaluated.

- No differences were observed in the MIC values obtained for the majority of the paired isolates.
- Against the *C. albicans* isolates identified at TOC, the ibrexafungerp MIC values ranged from 0.016 to 0.25 µg/mL; both studies showed MIC_{90} values of 0.12 µg/mL. In both studies, the ibrexafungerp MIC values against the *C. glabrata* ranged from 0.25 to 0.5 µg/mL with MIC_{90} values of 0.5 µg/mL.
- There were no significant differences in the MIC values obtained at the TOC compared to baseline isolates. No subject at the TOC visit had isolates with ibrexafungerp MIC greater than a 4-fold increase in MIC values compared to baseline. The exception was in the VANISH 303 clinical study; one subject with *C. albicans* had a TOC ibrexafungerp MIC value that 8-fold higher than the baseline (0.03 to 0.5 µg/mL) which was within the normal distribution observed for *C. albicans.*
- Molecular characterization of known mutations in the *fks* hot spot regions in *Candida* spp. was not performed.

Several subjects had different *Candida* spp. isolated at TOC from those identified at baseline in the ibrexafungerp group.

- In the SCY-078-303 clinical study, there were 3 subjects who had a different *Candida* isolate from that identified at baseline. Two subjects had *C. glabrata* at baseline and *C. albicans* at TOC. One subject had *C. albicans* infection at baseline and *C. glabrata* at TOC.
- In the SCY-078-306 clinical study, there were 5 patients who had a different isolate from that identified at baseline. The isolates identified at TOC included *C. albicans, C. glabrata, C. lipolytica, C. kefyr* and *C. tropicalis*.
- In both studies, the ibrexafungerp MICs were similar to subjects' MICs at baseline and TOC with similar organisms.

Overall, the ibrexafungerp MICs from the surveillance studies showed similar in vitro activity compared to isolates recovered from subjects with VVC. The majority of subjects had *C. albicans* isolated in the SCY-078-303 and SCY-078-306 trials. The MICs ranged from ≤0.016 – 0.25 µg/mL, with 58% of the subjects showing clinical cure and mycological eradication. However, subjects with *C. glabrata* infections in both clinical studies had MICs ranging from 0.12 – 1 µg/mL showing 48% clinical cure, with the majority of subjects (87%) showing persistence of infection and classified as microbiological failures. No conclusions could be made regarding ibrexafungerp efficacy against other types of *Candida* infections, since there were very few organisms.

It is important to note that pharmacokinetic studies indicate that following the protocol-specified 600 mg dose of ibrexafungerp under fasted state, the achievable C_{max} was 0.435

µg/mL and AUC 6.832 µg*h/mL (for further information see **Section 6).** A trend towards microbiological efficacy was associated with *C. albicans* isolates with MIC values ≤ 0.25 µg/mL. However, isolates such as *C. glabrata* with MIC values that were one dilution higher (≥ 0.5 µg/mL) correlated with mycological persistence. Therefore, the "first list" of microorganisms only includes *Candida albicans.* The second list which is based solely on in vitro data includes the following fungal organisms: *Candida auris, Candida dubliniensis, Candida glabrata, Candida guillermondii, Candida keyfr, Candida krusei, Candida lusitaniae, Candida parapsilosis,* and *Candida tropicalis.*

4.4. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ibrexafungerp is a novel triterpenoid antifungal compound intended for the treatment of VVC with dosing limited to BID oral doses of 300 mg in a single day. Oral-dose toxicology studies with ibrexafungerp included 1-month and 13-week studies in rats and dogs. The 1-month studies were conducted with the phosphate salt form of ibrexafungerp and the 13-week studies were conducted with the citrate salt form which is the ibrexafungerp form in the current clinical formulation. The 1-month studies included higher doses compared to the 13-week studies in both species, and more ibrexafungerp-related toxicities were apparent in the 1-month studies.

Several ibrexafungerp-related toxicities with potential clinical relevance occurred in a dose-dependent manner in the 1-month toxicology study in rats including degeneration of skeletal muscle cells and stomach glandular mucosa and single-cell necrosis of hepatocytes. Of these toxicities only degeneration of stomach glandular mucosa occurred in the 13-week toxicology study in rats and in the 1-month toxicology study in dogs. However, in the 13-week study in dogs, no stomach toxicity was observed with the highest administered dose of ibrexafungerp which was lower than the mid-dose in the 1-month toxicology study in dogs. Because stomach toxicity only occurred with repeated administration of high ibrexafungerp doses in rats and dogs, the single day of clinical dosing with the relatively low dose of ibrexafungerp planned for the treatment of VVC is not expected to be associated with persistent or progressive toxicity in the stomach. Similarly, the additional toxicities observed in the 1-month toxicology study in rats including skeletal muscle degeneration and single-cell necrosis of hepatocytes are not expected to be of clinical concern because the toxicities only occurred with administration of high doses resulting in plasma exposures many fold higher than the clinical exposure expected with the single-day, clinical-dosing regimen.

Findings consistent with multi-organ phospholipidosis were observed in all the 1-month and 13-week toxicology studies in both species. However, the degree of phospholipidosis was not associated with functional deficits or clear toxicities. Particularly, for the single day of ibrexafungerp administration planned for clinical treatment of VVC, phospholipidosis is not expected to pose a clinical concern.

Results from an in vitro hERG assay indicated that the ibrexafungerp IC_{50} for hERG inhibition was 1.4-fold higher than the plasma C_{max} value associated with the recommended clinical dose of 600 mg/day ibrexafungerp in fed patients. Also, in a cardiovascular study in conscious dogs, a single oral dose of 300 mg/kg ibrexafungerp produced a 6% reduction of QTc compared to control values 4-5 hours after dosing. However, in a Phase 1 clinical trial, ibrexafungerp in single IV doses did not prolong the QTc interval to a clinically relevant extent at plasma concentrations up to 5-fold higher than the concentrations achieved with the recommended clinical oral dose.

No other safety pharmacology findings including assessments of respiratory and CNS function were of clinical concern.

Ibrexafungerp was negative for genotoxicity in both nonclinical in vitro assays (Ames assays and a chromosome aberration assay in mammalian cells) and in vivo studies (micronucleus study in rat bone marrow cells). Carcinogenicity studies were not performed for ibrexafungerp due to the limited duration of its intended use for the treatment of VVC.

In a rabbit embryo-fetal study, serious and rare fetal malformations occurred primarily in one severely malformed mid-dose (25 mg/kg/day) fetus and in two severely malformed high-dose (50 mg/kg/day) fetuses in two different litters. Many of the malformations in the mid- and high-dose fetuses did not occur in any fetuses in the concurrent vehicle-control group or in comparable historical control data. Malformations included thoracogastroschisis (one mid- and one high-dose fetus), forelimb phocomelia (one mid- and one high-dose fetus), absent ear pinna (one mid- and one high-dose fetus), anencephaly (two high-dose fetuses in two litters), and absent hindpaw (one mid-dose fetus and two high-dose fetuses in two litters). Because several of the same malformations occurred in both the mid-dose and high-dose groups, ibrexafungerp-related malformations were considered to have occurred in both groups. The plasma AUC values associated with the No-Observed-Adverse-Effect Level (NOAEL) and Lowest-Observed-Adverse-Effect Level (LOAEL) doses in rabbits are approximately 2- and 5-times respectively the plasma AUC exposures expected for fed patients. The fetal malformation findings for ibrexafungerp and the associated exposure margins will be described in the product label.

In contrast to the results of the embryo-fetal study in rabbits, ibrexafungerp was not associated with fetal malformations in a rat embryo-fetal study. Also, ibrexafungerp did not inhibit male or female fertility in a fertility study in rats or produce adverse effects on the survival, growth, behavior, or reproductive ability of first-generation offspring in a pre-postnatal study in rats.

Oral bioavailability of the citrate salt form of ibrexafungerp was 22% and 26% for a 5 mg/kg dose in rats and dogs, respectively, with bioavailability increasing with a 20 mg/kg dose up to 35% in dogs and 48% in rats. In the 13-week toxicology studies in rats and dogs using ibrexafungerp citrate, plasma C_{max} and AUC values generally increased in a dose-proportional or less than dose-proportional manner and accumulation in plasma was evident with 2-3-fold higher AUC values at the end of dosing compared to the first day of dosing. Plasma $t_{1/2}$ values for ibrexafungerp citrate ranged from approximately 21 to 38 hours in rats and 7 to 11 hours in dogs. Ibrexafungerp was highly bound to plasma proteins with values of over 98% in all test species including humans. In a mass balance study in rats where [^{3}H]ibrexafungerp was administered in a single oral dose, the T_{max} for radioactivity in both plasma and blood was 4 hours with biphasic elimination. Extensive distribution to tissues was observed with the highest concentrations in large intestine, pituitary gland, bone marrow, and liver followed by lung and kidney, minimal concentrations in male reproductive organs, and no detectable radioactivity in brain and CNS tissues. The metabolism of ibrexafungerp was characterized in vitro in

incubations with microsomes and hepatocytes from multiple test species and humans as well an in vivo in rats and dogs. In incubations with [^{3}H]ibrexafungerp and human liver microsomes, two metabolites, M5 and M6, occurred as more than 10% of the total radioactivity added, but higher percentages of the two metabolites occurred in incubations with liver microsomes from dogs. A more extensive analysis identified 18 ibrexafungerp metabolites which were primarily oxidation and/or dehydrogenation products resulting from in vitro incubations with human, dog, or rat liver microsomes or intestinal microsomes from the same species. All the human metabolites were shown to occur in incubations with either liver or intestinal microsomes from either rats or dogs or from both species. In CYP inhibition/induction experiments using human liver microsomes, ibrexafungerp was shown to potently inhibit CYP2C8 activity, and more moderately inhibit CYP3A4 activity, but not induce the expression or activity of CYP3A4 or CYP1A. Following oral dosing, the primary route of ibrexafungerp excretion in rats was shown to be bile followed by feces with a much smaller percentage of excretion occurring in urine.

In summary, in nonclinical toxicology studies, ibrexafungerp was associated with toxicities that occurred with repeated dosing of high doses resulting in plasma exposures greatly in excess of the expected clinical exposures. Because ibrexafungerp will only be administered for one day for the treatment of VVC, the toxicities observed in the general toxicology studies in rats and dogs are not expected to be clinically relevant. A potential for QTc prolongation revealed in an assessment of ibrexafungerp inhibition of hERG activity is not expected to be a clinical concern based on the lack of QTc prolongation with high ibrexafungerp exposures in a Phase 1 study. Ibrexafungerp was associated with serious dose-related fetal malformations in rabbits at exposures 5- to 13-times the expected clinical exposure. These findings may have implications for the administration of ibrexafungerp to pregnant women and women of childbearing potential. Considering the nonclinical results as a whole, NDA 214900 is considered approvable from a Pharmacology/Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

IND 107521

5.3. Pharmacology

Safety pharmacology studies with ibrexafungerp (MK-3118 and SCY-078) included an in vitro hERG assay, a single intravenous-dose cardiovascular assessment in conscious dogs, and a single oral-dose cardiovascular and respiratory assessment in conscious dogs. In addition, a functional observational battery (FOB) was conducted in conjunction with the 1-month, oral-dose, toxicology study in rats.

Study Title: Electrophysiological Evaluation on hERG Channel Current Stably Expressed in CHO Cells. (Study No.: TT #09-4710).

Methods

This GLP-compliant study was conducted in 2009 by Merck Research Laboratories in Pennsylvania USA. CHO-K1 cells stably transfected with hERG channels were cultured then treated with vehicle (DMSO), MK-3118 (ibrexafungerp, phosphate salt) in concentrations of 0.3, 1, and 3 mcM (n = 4-8 cells per concentration; equivalent to 0.28, 0.92, and 2.77 mcg/ml respectively), or the positive control agent, cisapride in a concentration of 0.03 mcM. In voltage-clamped cells, hERG currents were activated and then current amplitude was monitored in the presence of vehicle for 1-5 minutes followed by increasing concentrations of MK-3118 or 0.03 mcM cisapride.

Results
MK-3118 inhibited hERG current reproducibly and in a concentration-dependent manner over the tested concentration range. Inhibition at nominal concentrations of 1 mcM (38% inhibition) and 3 mcM (86% inhibition) was statistically significant compared to vehicle control values. The positive control agent, cisapride, produced a 73.5% inhibition of hERG potassium channels which was within the historical control range of 34% to 83%. The estimated IC_{20} and IC_{50} values for MK-3118 inhibition of hERG channels were 0.5 (365 ng/ml) and 1.2 mcM (876 ng/ml) respectively. The clinical plasma C_{max} in fed patients has been estimated to be 629 ng/ml. Based on these values, the MK-3118 IC_{50} for hERG inhibition is approximately 1.4 times the expected human C_{max} values.

Study Title: An Intravenous Infusion Cardiovascular Safety Pharmacology Study Using Radiotelemetry in Conscious Beagle Dogs. (Study No.: SCY078-TOX-005)

Methods
In this GLP-compliant study performed by (b) (4) beginning in June 2015, conscious, telemetered Beagle dogs were used to assess cardiovascular safety for the new IV formulation of SCY-078 (ibrexafungerp). Single intravenous infusions (1 hour at 10 ml/kg/hour) of SCY-078 at doses of 0, 15, and 45 mg/kg were administered to 3 Beagle dogs using a Latin-Square design with a washout period of 6-7 days between successive doses. Plasma toxicokinetic data were collected for the high dose administration. Dogs were monitored for arterial blood pressure, electrocardiograms (heart rate, PR, QT and QTc intervals and QRS complex durations), body temperature, and locomotor activity over a telemetry recording period of at least 2 hours before the start of dosing and for at least 24 hours after the start of dosing. Values were calculated over 5 minutes and reported every 0.25 hours. In addition, a board-certified veterinary cardiologist examined and qualitatively assessed representative ECG tracings collected at approximately 1 hour before the start of infusion, 2 minutes before the end of infusion, and at 3, 6, and 24 hours after infusion.

Results
The morphology of the P-QRS-T waveforms remained normal with no significant changes in cardiac intervals with the 45 mg/kg dose of SCY-078. Also, no abnormalities were observed on the printed ECGs. Similar to what was observed following the administration of the vehicle and 15 mg/kg SCY-078, mean heart rate (HR) and mean systemic arterial blood pressure (SABP) increased slightly following the onset of infusion, but returned to near baseline levels by 1.25 hours after the start of infusion with 45 mg/kg SCY-078. Mean HR decreased by 18.0% on

average compared to the mean baseline levels between 1.25 and 2.75 hours after the start of dosing, but all HR values remained comparable to the baseline values that were less than 100 beats per minute. SABP decreased progressively to reach its lowest value (21.2% decrease compared to baseline) at 16.0 hours after the start of infusion, but this degree of decrease was similar to that measured for the vehicle administration (-23.8% at 18.5 hours after the start of infusion).

Study Title: Oral Cardiovascular and Respiratory Telemetry in Dogs. (Study No.: TT #09-5619).

Methods
This GLP-compliant study was conducted in 2009 by Merck Research Laboratories in PA USA. Four male Beagle dogs each received a single oral gavage dose of vehicle (0.5% methylcellulose) followed by increasing doses of MK-3118 (ibrexafungerp, phosphate salt) beginning with 30 mg/kg followed by 100 mg/kg and lastly 300 mg/kg with 7 days washout between doses. Dogs were previously implanted with Konigsberg solid-state pressure transducers with a biopotential lead for measurement of aortic blood pressure, heart rate, ECG parameters, body temperature, and respiratory function (respiratory rate and depth of respiration). The measured ECG parameters included: PR, QRS, RR, and QT intervals. QTc intervals were determined using Miyazaki Correction. Data were collected in 1-minute intervals from 2 hours before dosing (vehicle) or 20 hours before dosing (MK-3118 doses) until 72 hours after dosing.

Results
There were no test article-related effects on systolic, diastolic, and mean blood pressures after administration of 30, 100, and 300 mg/kg MK-3118 at any time over the 72-hour post dose collection. Also, no MK-3118-related changes in heart rate, RR interval, PR interval, or QRS interval occurred. A MK-3118-related decrease in QT interval and QTc interval with some reductions reaching statistical significance was observed with the high dose of 300 mg/kg/day compared to vehicle control values beginning 3 hours after dosing and continuing until about 12 hours after dosing. The peak reduction of QTc was -14 msec, (-6%) compared to the vehicle control value occurred 4-5 hours after dosing. No MK-3118-related changes in the rate of respiration, depth of respiration, or body temperature were observed. The NOAEL was considered to be 100 mg/kg/day, which based on body surface area comparison is approximately 5.6 times the expected clinical dose of 600 mg/day (10 mg/kg/day for an average human weighing 60 kg).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Single-dose Pharmacokinetics of SCY-078 in the Wistar Han Rat Following Intravenous and Oral Gavage	**IV Dosing with the SCY-078 Citrate Salt:** Plasma AUC values for SCY-078 increased in a roughly dose-proportional manner with similar mean values in males and females following IV dosing with the citrate salt form of ibrexafungerp. The plasma clearance (CL) values were low compared to hepatic blood flow in rats and decreased with dose in males but not in females. Plasma $t_{1/2}$ values increased with dose in

Type of Study	Major Findings
Administration./ Study No.: SCY-078-ADME-002	males from 7.6 hours at 5 mg/kg to 20.5 hours at 30 mg/kg but remained similar ranging from 11.4 to 13.5 hours in females. Mean volume of distribution (V_{dss}) for males (5.9 L/kg) and females (6.1 L/kg) was consistent with extravascular distribution (Table 5-1).

Table 5-1: Intravenous PK Results for SCY-O78 Administered in a Single Dose to Rats (Adapted from Table in the Study Report)

Group/ Dose	Gender	AUC_{0-24} (mcg•hr/ml)	AUC_{0-last} (mcg•hr/ml)	CL (L/kg/hr)	V_{dss} (L/kg/hr)	$T_{1/2}$ (hrs)
Group 1/ 5 mg/kg	Pooled	10.3	11.7	0.44	4.7	8.7
	Male	10.4	11.6	0.45	4.6	7.6
	Female	10.2	11.8	0.44	4.9	11.4
Group 2/ 15 mg/kg	Pooled	31.8	39.9	0.39	5.7	11 2
	Male	35.1	44.7	0.35	5.3	11.4
	Female	28.3	34.9	0.48	6.1	10.4
Group 3/ 30 mg/kg	Pooled	58.5	82.1	0.36	7.8	17.7
	Male	62.1	93.3	0.31	8.0	20 5
	Female	54.9	71.0	0.44	7.2	13 5

Oral Dosing with the SCY-078 Citrate and Phosphate Salts: Oral doses of 5, 15, and 40 mg/kg SCY-078 (citrate salt) resulted in plasma C_{max} and AUC values that increased in a greater than dose-proportional manner between the LD and MD and less than dose proportionally (C_{max}) or dose-proportionally (AUC) between the MD and HD (Table 5-2). Absolute oral bioavailability (F) was 22%, 48% and 45% for the 5, 20, and 40 mg/kg doses, respectively, in males with similar values in females. Plasma $t_{1/2}$ values were 6-10 hours in males and 9-11 hours in females.

Following oral administration of 5 and 40 mg/kg/day SCY-078 (phosphate salt), plasma AUC exposure increased in a more than dose-proportional manner in males and in a roughly dose-proportional manner in females (Table 5-2). Plasma C_{max} and AUC values were less than half of those observed following oral dosing with the SCY-078 citrate salt for the 40 mg/kg dose. Plasma $t_{1/2}$ was on the order of 10 hours with the HD in both sexes, and oral bioavailability was 14% and 16% at the 5 and 40 mg/kg dose levels, respectively. The oral bioavailability with the phosphate salt was about 2/3 of that of the citrate salt at the 5 mg/kg dose and less than half of the oral bioavailability for the citrate salt at the 40 mg/kg dose.

Table 5-2: Oral PK Results for SCY-O78 Administered in a Single Dose to Rats (Adapted from Table in the Study Report)

Group/ Dose	Gender	C_{max} (mcg/ml)	AUC_{0-last} (mcg•hr/ml)	$T_{1/2}$ (hrs)	F (%)	CL/F (L/kg/hr)
Group 4/ 5 mg/kg (citrate)	Pooled	0.177	2.39	7.6	22	1.99
	Male	0.203	2.33	6.1	22	2.09
	Female	0.182	2.44	9.1	23	1.88
Group 5/ 20 mg/kg (citrate)	Pooled	1.01	20.6	9.1	45	0.96
	Male	1.02	21.3	8.6	48	0.93
	Female	1.16	20.0	9.6	44	0.99
Group 6/ 40 mg/kg (citrate)	Pooled	1.70	39.5	10.3	43	1.00
	Male	1.48	39.6	9.9	45	1.00
	Female	1.93	39.3	10.7	43	1.00
Group 7/ 40 mg/kg (phosphate)	Pooled	0.156	1.48	----	14	3.05
	Male	0.131	1.02	----	9	4.82
	Female	0.180	1.93	----	20	2.16
Group 8/	Pooled	0.870	14.8	9.6	16	2.68

Type of Study	Major Findings
	40 mg/kg (phosphate) Male 0.800 14.1 9.3 16 2.82 40 mg/kg (phosphate) Female 0.978 15.5 10.2 17 2.55
Single-Dose Pharmacokinetics of SCY-078 in the Beagle Dog Following Intravenous and Oral Gavage Administration/ Study No: SCY-078-ADME-003	**IV Dosing with the SCY-078 Citrate Salt:** SCY-078 plasma AUC exposure increased in a dose-proportional manner following single IV doses of 5, 15, and 30 mg/kg SCY-078 in Beagle dogs. Plasma clearance was about 20% of hepatic blood flow in dogs (1.85 L/kg/hr) ranging from 0.28 to 0.58 L/kg/hr with similar results for males and females. Clearance did not change with dose, but plasma $t_{1/2}$ values did increase with dose with average values for both sexes of 9.3, 15.0, and 17.9 hours for the 5, 15, and 30 mg/kg doses. The estimated volume of distribution values were much lower than the estimated plasma volume for dogs, but comparable for both sexes and increased with dose with values of 5.1, 6.1, and 8.4 L/kg for the 5, 15, and 30 mg/kg doses. Concentration-time profiles with variable infusion times for a 5 mg/kg dose of the SCY-078 citrate salt indicated that plasma C_{max} and AUC values remained similar regardless of infusion time. **Oral Dosing with the SCY-078 Citrate Salt:** Following single oral doses of 5, 20, and 40 mg/kg SCY-078 citrate salt, plasma AUC values increased in a roughly dose-proportional manner between the LD and MD, but plateaued at the HD. The absolute oral bioavailability for the SCY-078 citrate salt for males and females combined was 26%, 35%, and 24% for the 5, 20, and 40 mg/kg doses. Plasma $t_{1/2}$ values were consistent with values of 10.2, 15.2, and 12.7 hours for the 5, 20, and 40 mg/kg doses, respectively. **Oral Dosing with the SCY-078 Phosphate Salt:** The oral bioavailability of the phosphate salt was notably lower compared to citrate salt oral bioavailability with phosphate salt values of 14% and 24% for the 5 and 40 mg/kg doses. Other values, including plasma $t_{1/2}$ and clearance, were similar for the two salts. **Effect of Pentagastrin Pretreatment:** No clear trend occurred for oral bioavailability or other pharmacokinetic parameters for the SCY-078 citrate (doses of 5, 10, and 20 mg/kg/day) or phosphate salts (dose of 20 mg/kg/day) when the test animals were pre-treated with pentagastrin. These results suggest gastric acidity did not affect the oral bioavailability of SCY-078 in a consistent manner.
Distribution	
MK-3118 In Vitro Drug Metabolism Studies./ Study No.: PK002	**In Vitro Plasma-Protein Binding and Blood-to-Plasma Partitioning:** The unbound fraction of MK-3118 in plasma was 0.7-0.9% in rat, dog, monkey, and human, and 1.7–2.1% in mouse over a concentration range of 0.5-20 mcM. The blood to-plasma partition ratio was 0.5-0.6 in all species over the same concentration range.
Pharmacokinetics, Mass Balance, and Tissue Distribution of Radioactivity in Male Intact and Bile-Duct Cannulated Sprague-Dawley Rats Administered a Single Oral Dose of [^{3}H]SCY-078./ Study No.: SCY-078-ADME-001	Following a single oral dose of [^{3}H]SCY-078, the T_{max} for radioactivity in both plasma and blood was 4 hours and C_{max} values were 229 and 171 ng-eq/g respectively. Elimination was biphasic with an initial steep decline through 24 hours and a more gradual decline thereafter. The lower blood levels compared to plasma reflect low red blood cell portioning and blood to plasma ratios ranging from 0.71 at 30 minutes to 0.95 at 120 hours after dosing. The tissues with the greatest radioactivity concentrations detected by quantitative whole-body radiography (highest to lowest) were large

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>intestine, pituitary gland, bone marrow, liver, lymph nodes, lung, adrenal gland, thyroid gland, thymus, and kidney. Minimal concentrations were detected (highest to lowest) in preputial gland, prostate gland, seminal vesicles, epididymis, and testes. No radioactivity was detected in the brain, eye or CNS tissues including the spinal cord.</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>Study Title: MK-3118 In Vitro Drug Metabolism Studies./Study No.: PK002</td><td>Metabolism in Liver Microsomes and Hepatocytes: [^{3}H]MK-3118 metabolism was assessed in pooled microsome preparations and cryopreserved hepatocytes from DBA mice, Sprague Dawley rats, Beagle dogs, Cynomolgus monkeys and/or humans. Metabolism was minimal in incubations with mouse and rat liver microsomes. In contrast, the compound was subject to extensive hydroxylation in incubations with liver microsomes from dogs, monkeys, and humans. Parent glucuronidation was observed in incubations with hepatocytes from dogs, monkeys, and humans. Sulfation of a hydroxylated metabolite was detected in incubations with monkey and human hepatocytes. All metabolites observed in human liver microsomes and hepatocytes were detected in liver microsomes/hepatocytes from preclinical species indicating adequate metabolite coverage for the disproportionate human metabolites (Table 5-3 and Table 5-4).

Human liver microsomal incubations with MK-3118 conducted in the presence of anti-CYP3A4 antibody resulted in more than 90% inhibition of the metabolism of MK-3118, while other anti-CYP antibodies (anti-CYP2C8 and anti-CYP2C9) had little inhibition effects on metabolism of MK-3118. These data suggest that the oxidative metabolism of MK-3118 in human liver microsomes is mainly mediated by CYP3A4.

Table 5-3: In Vitro Metabolism of [^{3}H]MK-3118 in Liver Microsomes of Human and Preclinical Species. (Table from the Study Report)
<table>
<tr><th></th><th colspan="9">Turnover (% of Total Radioactivity)</th></tr>
<tr><th>Species</th><th>M2</th><th>M3</th><th>M4</th><th>M5</th><th>M6</th><th>M8</th><th>M9</th><th>M10</th><th>MK-3118</th></tr>
<tr><td>Mouse</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>100</td></tr>
<tr><td>Rat</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>100</td></tr>
<tr><td>Dog</td><td>4</td><td></td><td>43</td><td>25</td><td>4</td><td>7</td><td>1</td><td>4</td><td>12</td></tr>
<tr><td>Monkey</td><td>–</td><td>18</td><td>52</td><td>12</td><td>2</td><td>6</td><td>1</td><td>2</td><td>7</td></tr>
<tr><td>Human</td><td>3</td><td>7</td><td>34</td><td>13</td><td>4</td><td>4</td><td>6</td><td>4</td><td>26</td></tr>
</table>
[a] [^{3}H]MK-3118 (10 µM) was incubated with liver microsomes (1 mg protein/mL) at 37°C for 60 min in the presence of NADPH.

Table 5-4: In Vitro Metabolism of [^{3}H]MK-3118 in Liver Microsomes of Human and Preclinical Species. (Table from the Study Report)
<table>
<tr><th></th><th colspan="9">Turnover (% of Total Radioactivity)</th></tr>
<tr><th>Species</th><th>M1</th><th>M4</th><th>M5</th><th>M6</th><th>M7</th><th>M8</th><th>M9</th><th>M10</th><th>MK-3118</th></tr>
<tr><td>Mouse</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>100</td></tr>
<tr><td>Rat</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>100</td></tr>
<tr><td>Dog</td><td>–</td><td>28</td><td>19</td><td>3</td><td>3</td><td>2</td><td>1</td><td>1</td><td>43</td></tr>
<tr><td>Monkey</td><td>17</td><td>8</td><td>17</td><td>8</td><td>2</td><td>2</td><td>1</td><td>–</td><td>44</td></tr>
<tr><td>Human</td><td>4</td><td>2</td><td>2</td><td>1</td><td>3</td><td>–</td><td>–</td><td>1</td><td>88</td></tr>
</table>
[a] [^{3}H]MK-3118 (10 µM) was incubated with hepatocytes (1 million cells/mL) at 37°C for 2 hr.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>CYP Inhibition: In reversible inhibition assays using pooled human liver microsomes, MK-3118 potently inhibited CYP2C8 activity (IC_{50} = 1.5 mcM), and moderately inhibited CYP3A4 (IC_{50} = 7.2 mcM). The IC_{50} for all other CYPs investigated (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6) was > 10 mcM. In experiments measuring time-dependent inhibition of CYP3A4 activity, MK-3118 in concentrations of 10 and 50 mcM did not inhibit CYP3A4 activity, but the positive control agent, mifepristone, produced time-dependent inhibition relative to the solvent control.

CYP3A4 Induction: In 48-hour incubations with cultures from cryopreserved human hepatocytes, MK-3118 caused no significant induction of CYP3A4 mRNA, whereas the positive control, rifampicin, induced CYP3A4 mRNA by 13.1- to 19.5-fold. In addition, MK-3118 caused no induction of CYP3A4 activity, while the positive control agent, rifampicin, induced CYP3A4-mediated testosterone 6β-hydroxylation with a response ranging from 8.0- to 13.2-fold.

CYP1A2 Induction: In incubations with cultures from cryopreserved human hepatocytes, MK-3118 caused no induction of CYP1A2 mRNA, whereas the positive control, omeprazole, induced CYP1A2 mRNA 41.3- to 106.7-fold across the hepatocyte lots tested. Omeprazole was also a potent inducer of CYP1A2-mediated phenacetin O-deethylation with a response ranging from 8.2- to 37.5-fold. MK-3118 caused no significant induction of CYP1A2 activity in the same assay.</td></tr>
<tr><td>Study Title: In Vivo Metabolism and Excretion of [^{3}H]MK-3118 in Rats./ Study No.: PK003</td><td>In Vivo Metabolism: The metabolites detected in rat bile, urine, and feces are summarized in Table 5-5. In bile, two metabolites (M7 and M9) occurred at above 15% of the total IV dose. For the oral dose, M7 occurred again at about 15% of the total dose, but the amount of M9 was lower at about 3% of the total dose. M7 was characterized as a glucuronic acid metabolite, and M9 was the major oxidative metabolite with three other oxidative metabolites (M11, M12, and M13) occurring at lower levels in bile. No metabolites or the parent compound were detected in urine, and only the parent compound was detected in feces.

Table 5-5: Percent [^{3}H]SCY-078 Excreted as Parent Compound or Metabolites in Bile, Urine, and Feces of Male Rats. (Table from the Study Report)
<table>
<tr><th rowspan="2">Route (Dose)</th><th></th><th colspan="6">% of Total Dose</th></tr>
<tr><th></th><th>Parent</th><th>M7</th><th>M9</th><th>M11</th><th>M12</th><th>M13</th></tr>
<tr><td rowspan="3">IV[a] (2 mg/kg)</td><td>Bile</td><td>16.2</td><td>19.3</td><td>16.6</td><td>2.1</td><td>4.3</td><td>6.5</td></tr>
<tr><td>Urine</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Feces</td><td>11.0</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td rowspan="3">P.O.[b] (5 mg/kg)</td><td>Bile</td><td>4.6</td><td>14.6</td><td>3.3</td><td></td><td>0.8</td><td>1.0</td></tr>
<tr><td>Urine</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Feces</td><td>30.0</td><td>-</td><td></td><td>-</td><td>-</td><td>-</td></tr>
</table>
[a] Male rats were dosed intravenously at 2 mg/kg with [^{3}H]MK-3118 (n=3).
[b] Male rats were dosed orally at 5 mg/kg with [^{3}H]MK-3118 (n=3).
Notebook/Pages: 0278053/0025.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Qualitative Comparison of SCY-078 Metabolite Profiles in Rat and Dog Plasma after Oral and Intravenous Delivery, and In Vitro Following Incubation with Rat and Dog and Human Hepatic and Intestinal Microsomes./ Study No.: SCY-078-ADME-007</td><td>
In Vitro Studies: Metabolism was more extensive in liver microsomes compared to intestinal microsomes for all species, and overall metabolism in terms of the quantities of metabolites as well as the range of metabolites was greatest in dog microsomes compared to human microsomes with the least metabolism occurring in rat microsomes. The metabolic changes consisted mainly of single oxidations, di-oxidations, and dehydrogenations. All human in vitro metabolites were observed with rat or dog microsomes (Table 5-6).

Table 5-6: Metabolites Following Incubation of SCY-078 Citrate with Rat, Dog, and Human Liver and Intestinal Microsomes. (Adapted from Table in the Study Report)
<table>
<tr><th>Parent or Metab.</th><th>Proposed Biotransformation</th><th>HLM</th><th>HIM</th><th>DLM</th><th>DIM</th><th>RLM</th><th>RIM</th></tr>
<tr><td>SCY-078</td><td>Parent</td><td colspan="6"></td></tr>
<tr><td>M1</td><td>Di-oxidation</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M2</td><td>Di-oxidation</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M3</td><td>Di-oxidation</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M6</td><td>Di-oxidation</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M8</td><td>Di-oxidation + dehydrogenation</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M9</td><td>Di-oxidation</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M11</td><td>Di-oxidation + dehydrogenation</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M12</td><td>Oxidation (Ox1)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>M13</td><td>Oxidation (Ox2)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M14</td><td>Oxidation (Ox3)</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M16</td><td>Di-oxidation + dehydrogenation</td><td>X</td><td></td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M20</td><td>oxidation + dehydrogenation</td><td>X</td><td></td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M21</td><td>oxidation + dehydrogenation</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M22</td><td>oxidation + dehydrogenation</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td></td></tr>
<tr><td>M23</td><td>oxidation + dehydrogenation</td><td>X</td><td>X</td><td>X</td><td></td><td></td><td></td></tr>
<tr><td>M24</td><td>Oxidation (Ox4)</td><td>X</td><td>X</td><td>X</td><td></td><td>X</td><td>X</td></tr>
<tr><td>M25</td><td>Dehydrogenation</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>M27</td><td>Oxidation (Ox5)</td><td>X</td><td>X</td><td>X</td><td></td><td>X</td><td></td></tr>
</table>

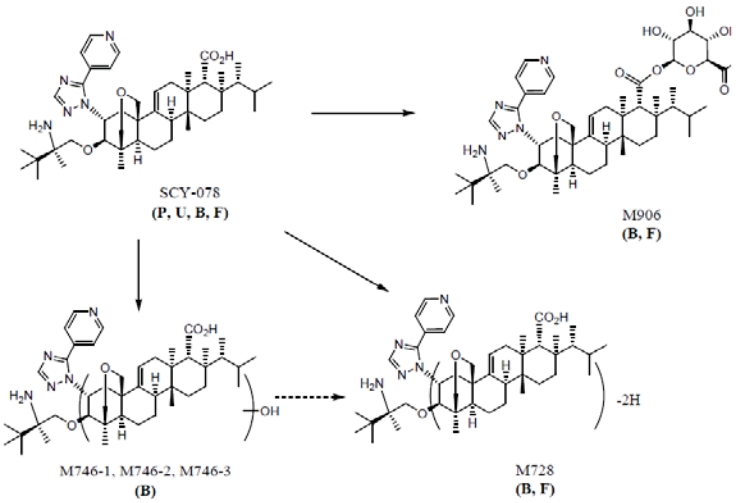
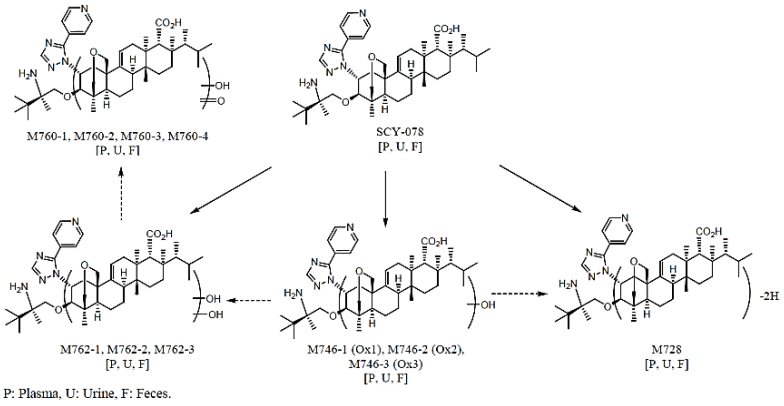
Following single oral and IV doses of SCY-078 citrate salt, more metabolism occurred after oral dosing compared to IV dosing, and the primary metabolites for both routes of administration were M12, M14, and M15 (Table 5-7).
</td></tr>
</table>

Type of Study	Major Findings

Table 5-7: Metabolites Detected in Dog Plasma Following Single Oral (40 mg/kg) and IV (15 mg/kg) Doses of SCY-078 Citrate Salt. (Table from the Study Report)

Analyte	Δ MW	Proposed Biotransformation	% of Total AUC PO	% of Total AUC IV
SCY-078	0	Parent	34.9	71.5
M14	16	Oxidation (Ox2)	18.9	5.4
M12	16	Oxidation (Ox1)	10.9	8.9
M15	16	Oxidation (Ox3)	7.4	2.1
M16	30	Dioxidation + Dehydrogenation	4.0	2.0
M13	30	Dioxidation + Dehydrogenation	3.7	0.3
M25	-2	Dehydrogenation	3.5	4.0
M21	14	Oxidation + Dehydrogenation	3.3	0.5
M19	176	Glucuronidation	2.9	0.6
M11	30	Dioxidation + Dehydrogenation	2.7	0.2
M22	14	Oxidation + Dehydrogenation	1.1	0.9
M24	16	Oxidation (Ox4)	1.0	1.4
M27	16	Oxidation (Ox5)	1.0	0.4
M17	176	Glucuronidation	0.9	0.4
M8	30	Dioxidation + Dehydrogenation	0.8	0.2
M6	32	Di-oxidation	0.7	0.2
M18	32	Di-Oxidation	0.4	0.2
M7	192	Oxidation + Glucuronidation	0.4	0.1
M20	14	Oxidation + Dehydrogenation	0.3	0.1
M2	32	Di-oxidation	0.3	<0.1
6	14	Oxidation + Dehydrogenation	0.2	0.4
M1	32	Di-oxidation	0.2	<0.1
M10	32	Di-oxidation	0.1	<0.1
M23	14	Oxidation + Dehydrogenation	0.1	0.1
M9	32	Di-oxidation	0.1	<0.1
M3	32	Di-oxidation	0.1	<0.1
M5	192	Oxidation + Glucuronidation	<0.1	<0.1
M4	192	Oxidation + Glucuronidation	<0.1	<0.1

Note: <0.1% is below the limit of detection

Type of Study	Major Findings
Study Title: Metabolite Profiling and Identification in the Rat Plasma, Urine, Bile, and Feces Following a Single Oral or Intravenous Dose of [14C]SCY-078./ Study No.: SCY078-ADME-043	 **P: Plasma, U: Urine, B: Bile, F: Feces** **Figure 1: Proposed Metabolic Products of [^{14}C]SCY-078 in Han Wistar Rats. (Figure from the Study Report)**
Study Title: Metabolite Profiling and Identification in the Dog Plasma, Urine, and Feces Following a Single Oral or Intravenous Dose of [^{14}C]SCY-078./ Study No.: SCY078-ADME-044	 **P: Plasma, U: Urine, F: Feces** **Figure 2: Proposed Metabolic Products of [^{14}C]SCY-078 in the Plasma, Urine, and Feces of Beagle Dogs. (Figure from the Study Report)**
Excretion	
Study Title: Pharmacokinetics, Mass Balance, and Tissue Distribution of Radioactivity in Male Intact and Bile-Duct Cannulated Sprague-Dawley Rats Administered a Single Oral Dose of [^{3}H]SCY-078./ Study No.: SCY-078-ADME-001	The primary route of elimination was fecal excretion with a mean fecal recovery of radioactivity through 96 hours after dosing of approximately 90%. Urinary excretion was very minimal with less than 0.2% recovery in urine after 96 hours.

Type of Study	Major Findings
Study Title: In Vivo Metabolism and Excretion of [^{3}H]MK-3118 in Rats./ Study No.: PK003	**Excretion of Radioactivity:** After oral dosing, 26%, 0.4%, and 30% of the radioactivity was excreted in bile, urine, and feces, respectively, with a total recovery of 57% over 48 hours. Following IV dosing, 68%, 0.8% and 11% of the administered radioactivity was recovered in bile, urine, and feces respectively with a total recovery of 80% over 48 hours. In rat bile, which was the major route of excretion, 5-16% of the radioactive dose was determined to be intact parent compound regardless of the route of administration.
TK data from general toxicology studies	
Study Title: One-Month Oral Toxicity Study in Rats with a Functional Observational Battery (FOB)./ Study No.: TT #09-1092 **(ibrexafungerp phosphate salt)**	**Plasma TK values for SCY-078 from Week 5 of dosing** 40 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 3.80 mcM (2774 ng/ml); AUC_{0-24hr} = 44.1 mcM•hr (32195 ng•hr/ml) 80 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 5.22 mcM (3811 ng/ml); AUC_{0-24hr} = 83.7 mcM•hr (61106 ng•hr/ml) 200 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 6.77 mcM (4942 ng/ml); AUC_{0-24hr} = 149 mcM•hr (108778 ng•hr/ml) Accumulation: Not assessed. TK measurements were performed in Week 5 only. Dose proportionality: Plasma AUC_{0-24hr} values increased approximately dose-proportionally between 40 and 80 mg/kg/day and less than dose-proportionally between 80 and 200 mg/kg/day. Plasma C_{max} values increased in a less than dose-proportional manner for all doses.
Study Title: A 13-Week Study of SCY-078 by Oral Gavage in Rats with a 14-day Recovery Period./ Study No.: SCY078-TOX-011 **(ibrexafungerp citrate salt)**	**Plasma TK values for SCY-078 from Day 91 of dosing** 20 mg/kg/day: $T_{1/2}$ = 20.9 hours in females; C_{max} = 1723 ng/ml in males and 2450 ng/ml in females; AUC_{0-24hr} = 28798 ng•hr/ml in males and 35389 ng•hr/ml in females. 40 mg/kg/day: $T_{1/2}$ = 37.8 hours in females; C_{max} = 3613 ng/ml in males and 4567 ng/ml in females; AUC_{0-24hr} = 65578 ng•hr/ml in males and 84685 ng•hr/ml in females. 80 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 4665 ng/ml in males and 4767 ng/ml in females; AUC_{0-24hr} = 95703 ng•hr/ml in males and 104852 ng•hr/ml in females. Accumulation: Day 91 AUC values were 2.11 to 3.17-fold higher than Day 1 AUC values consistent with plasma accumulation of SCY-078. Dose proportionality: Plasma C_{max} and AUC_{0-24hr} values increased approximately dose-proportionally between 20 and 40 mg/kg/day and less than dose-proportionally between 40 and 80 mg/kg/day.
Study Title: One-Month Oral Toxicity Study in Dogs./ Study No.: TT #09-1091 **(ibrexafungerp phosphate salt)**	**Plasma TK values from Week 5 of dosing** 30 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 2.81 mcM (2051 ng/ml); AUC_{0-24hr} = 32.9 mcM•hr (24019 ng•hr/ml) 100 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 4.41 mcM (3220 ng/ml); AUC_{0-24hr} = 76.0 mcM•hr (55484 ng•hr/ml) 300 mg/kg/day: $T_{1/2}$ = not calculated; C_{max} = 6.57 mcM (4796 ng/ml); AUC_{0-24hr} = 116 mcM•hr (84687 ng•hr/ml) Accumulation: Plasma C_{max} and AUC values were approximately 2-3 fold higher in Week 5 of dosing compared to Day 1 consistent with plasma accumulation of SCY-078. Dose proportionality: Plasma C_{max} and AUC_{0-24hr} values increased in a less than dose-proportional manner.
Study Title: A 13-Week Study of SCY-078 by Oral	**Plasma TK values from Day 91 of dosing** 15 mg/kg/day: C_{max} = 580 ng/ml in males and 852 ng/ml in females;

Type of Study	Major Findings
Gavage in Dogs with a 14-day Recovery Period./ Study No.: SCY078-TOX-012 **(ibrexafungerp citrate salt)**	$AUC_{0\text{-}24hr}$ = 6698 ng•hr/ml in males and 8465 ng•hr/ml in females. 30 mg/kg/day: C_{max} = 1128 ng/ml in males and 1785 ng/ml in females; $AUC_{0\text{-}24hr}$ = 13932 ng•hr/ml in males and 26814 ng•hr/ml in females. 60 mg/kg/day: C_{max} = 2746 ng/ml in males and 1917 ng/ml in females; $AUC_{0\text{-}24hr}$ = 39779 ng•hr/ml in males and 27413 ng•hr/ml in females. Plasma $t_{1/2}$: reportedly ranged from 7.23 to 10.7 hours. Accumulation: Plasma C_{max} and AUC values tended to increase slightly with the duration of dosing in the mid- and high-dose groups with consistently higher values on Day 91 compared to Days 1 and 15. Dose proportionality: Overall, plasma C_{max} and AUC values for SCY-078 increased in a less dose-proportional to approximately dose-proportional manner.
TK data from reproductive toxicology studies	
Study Title: An Embryo-Fetal Development Study of SCY-078 by Oral (Gavage) in Rats./ Study No.: SCY078-TOX-023 **(Ibrexafungerp citrate salt)**	**Rat (Toxicokinetic values on GD 17)** 10 mg/kg/day dose: plasma C_{max} = 617 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 9620 ng•hr/ml 20 mg/kg/day dose: plasma C_{max} = 1100 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 16000 ng•hr/ml 35 mg/kg/day dose: plasma C_{max} = 1730 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 30100 ng•hr/ml 50 mg/kg/day dose: plasma C_{max} = 2630 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 50900 ng•hr/ml
Study Title: An Embryo-Fetal Development Study of SCY-078 by Oral (Stomach Tube) in Rabbits./ Study No.: SCY078-TOX-024 (ibrexafungerp citrate salt)	**Rabbit (Toxicokinetic values on GD 19)** 10 mg/kg/day dose: plasma C_{max} = 1580 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 18300 ng•hr/ml 25 mg/kg/day dose: plasma C_{max} = 4200 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 52100 ng•hr/ml 50 mg/kg/day dose: plasma C_{max} = 8780 ng/ml; plasma $AUC_{0\text{-}24hr}$ = 133000 ng•hr/ml

5.5. Toxicology

5.5.1. General Toxicology

Oral-dose toxicology studies with ibrexafungerp included 1-month and 13-week studies in rats and dogs. The 1-month studies were conducted with the phosphate salt form of ibrexafungerp and did not include recovery periods. The 13-week studies were conducted with the citrate salt form which is the ibrexafungerp form in the current clinical formulation and these studies included 14-day recovery periods.

Study title/ number: One-Month Oral Toxicity Study in Rats with a Functional Observational Battery (FOB)./ TT #09-1092

- MK-3118-related histopathology included skeletal muscle degeneration in high-dose males and females, degeneration of stomach glandular mucosa in mid- and

high-dose males and females, and single-cell necrosis of hepatocytes in mid- and high-dose females.

- Prothrombin time and/or activated partial thromboplastin time were significantly reduced, and fibrinogen levels and/or platelets were significantly increased in high-dose males and females.
  - The NOAEL value was considered to be the low dose of 40 mg/kg/day which was associated with plasma C_{max} and AUC values for MK-3118 of 3.8 mcM (2.8 mcg/ml) and 44.1 mcM•hr (32.2 mcg•hr/ml) respectively.

Conducting laboratory and location: Merck Research Laboratories, PA, USA
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Doses of 0 (Group 1, vehicle control), 40 (Group 2, LD), 80 (Group 3, MD), and 200 (Group 4, HD) mg/kg/day administered once per day.
Route of administration:	Oral gavage
Formulation/Vehicle:	MK-3118 (ibrexafungerp; phosphate salt) was dissolved in a vehicle of 10% Polysorbate 80 in deionized water.
Species/Strain:	Rat, Wistar Han
Number/Sex/Group:	10/sex/group
Age:	Approximately 5 weeks
Satellite groups/ unique design:	Male and female rats were administered vehicle or 40, 80, or 200 mg/kg/day of the phosphate salt form of MK-3118 by oral gavage for 30 days, followed by animal euthanasia on Day 31.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No deaths were attributed to administration of MK-3118.
Clinical Signs	In the MD and HD groups, MK-3118-related clinical signs included an increased incidence of salivation in males (6/10 MD and 10/10 HD) and females (9/10 MD and 10/10 HD). No control or LD animals exhibited increased salivation.
Body Weights	Mean body weights were similar throughout the study for all groups. HD males and females had decreased body weight gain (-24% in males and -22% in females) in Week 5 compared to vehicle control values.
Ophthalmoscopy	No MK-3118-related changes in any ophthalmoscopy parameters were observed.
Hematology	The statistically significant changes in hematology parameters shown below did not have clear toxicological relevance.

	HD females: +508% neutrophil counts*, +164% monocyte counts*, +69% leukocyte counts*, +17% platelets, +34% fibrinogen*, -9.8% APTT* MD females: +40% neutrophils*, +22% fibrinogen* HD males: +288% neutrophil counts*, +75% monocyte counts, +34% leukocyte counts, +20% platelets*, +50% fibrinogen*, -11.1% prothrombin time*, -18.8% APTT*.
Clinical Chemistry	The changes in serum chemistry parameters shown below were not of sufficient magnitude to be considered toxicologically relevant. HD females: +52% AST*, +183% ALT*, +84% triglycerides*, -17% BUN*, +17% potassium*, +12% phosphorus*, +52% cholesterol* MD females: +9.8% potassium*, +39% triglycerides*, -11% BUN*, +48% cholesterol* HD males: +126% ALT*, +8.8% potassium*
Urinalysis	No MK-3118-related changes in any urinalysis parameters were observed.
Gross Pathology	No gross pathology findings were reported.
Organ Weights	The absolute weights of heart, pituitary, ovary, and thymus were decreased in HD females as well as relative pituitary weight (% of body and brain weight), ovary weight (% of brain weight) and thymus weight (% of brain weight). In HD males, absolute brain, thymus, and prostate weights were decreased. Relative prostate weights (% of brain weight) were significantly reduced in males in all the MK-3118 treatment groups with the greatest reductions in HD males compared to control values. Other organs had increased weights including relative liver weights (% of body weight) in HD females and relative liver and kidney weights (% of body weight) in HD males (Table 5-8). Some of the organ-weight gains correlated with histopathology or phospholipidosis in the affected organs.

Table 5-8: Organ Weights in the 1-month Study in Rats.

Organ (Weight Category)	Group 1 (VC)	Group 2 (LD)	Group 3 (MD)	Group 4 (HD)
Females				
Heart (AW- grams)	0.73	0.71	0.65*	0.65 *
Liver (% of BW)	3.00	3.14	3.20	3.57 ***
Pituitary (AW- grams)	0.0094	0.0095	0.0088	0.0067 ***
Pituitary (% of BW)	0.0058	0.0058	0.0057	0.0046 ***
Pituitary (% of BRW)	0.561	0.547	0.527	0.398 ***
Ovary (AW – grams)	0.0968	0.0867	0.0824	0.0751 *
Ovary (% of BRW)	5.77	5.01	4.96	4.43 *
Thymus (AW – grams)	0.47	0.41	0.39	0.33 *
Thymus (% of BRW)	28.45	24.23	23.84	19.85 *

	Males Brain (AW – grams): 1.86 / 1.87 / 1.80 / 1.74 * Kidney (% of BW): 0.821 / 0.858 / 0.839 / 0.937 *** Liver (% of BW): 3.13 / 3.02 / 3.08 / 3.41 ** Prostate (AW-grams): 0.31 / 0.25 / 0.23 / 0.19 ** Prostate (% of BRW): 17 / 13 * / 13* / 11 * Thymus (AW – grams): 0.51 / 0.53 / 0.50 / 0.40 * AW = absolute weight; BW = body weight; BRW = brain weight * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$
Histopathology Adequate battery: Yes	Histopathology findings in skeletal muscle, stomach, liver, and lymph nodes were considered related to MK-3118 administration. **Skeletal Muscle:** Skeletal muscle degeneration, primarily in the rectus femoris, was observed in HD animals with moderate severity in HD females and very slight to moderate severity in HD males. Within the affected muscles, a variable number of hyper-eosinophilic and/or vacuolated myocytes were observed as well as myocyte regeneration that was characterized by centralized nuclei with basophilic sarcoplasm and histiocytic cells in the interstitium. **Stomach:** Very slight to moderate degeneration of the glandular mucosa of the stomach was present in MD and HD male and female rats with the greatest incidence in HD animals. The findings were characterized by attenuation of parietal and chief cells and disorganization and collapse of glandular mucosa. In MD females, the degeneration was very slight and primarily characterized by decreased basophilia of chief cells. **Liver:** Single-cell necrosis of hepatocytes of very slight to slight severity was observed in 2/10 MD females and 7/10 HD females. The liver findings primarily occurred in centrilobular regions and were characterized by shrunken, hypereosinophilic hepatocytes with pyknotic nuclei and associated infiltrations of mixed inflammatory cells primarily composed of mononuclear cells. **Mesenteric Lymph Node:** A few HD rats exhibited inflammation in mesenteric lymph nodes with moderate severity in 2/10 HD females and slight to marked severity in 4/10 HD males. The inflammation correlated with enlarged lymph nodes in 1 HD female and 2 HD males. The inflammation was characterized by one or more central cores of necrotic cell debris surrounded by mononuclear cells and an early fibrovascular response. **Thymus:** Very slight lymphoid necrosis in the thymus was observed in 3/10 HD males and moderate lymphoid necrosis was observed in 1/10 HD females. These findings are consistent with stress, and the Sponsor considered the findings to be secondary to histiocytosis in lymph nodes.

	Non-adverse Phospholipidosis: Findings of vacuolation and histiocytosis consistent with phospholipidosis were observed in multiple tissues including liver, small intestine, lung, lymph node, and spleen. Vacuolation and histiocytosis findings were increased in incidence in a MK-3118-dose-dependent manner. Histiocytosis in the epithelium of the biliary tract, lymph nodes, and lung included foamy macrophages. The severity of the findings was very slight to slight except in mesenteric and cervical lymph nodes where the severity ranged from very slight to moderate in HD males and females.
[Other evaluations]	**Toxicokinetics:** see Section 5.4 **Functional Observational Battery:** On Day 1 following the first dose, the first 6/10 males in each group were evaluated for home-cage, hand-held, and open-field observations, stimulus-activity responses, and other parameters including forelimb and hindlimb grip strength. None of the doses of MK-3118 produced significant changes in any of the measured parameters compared to control values. **Serum Gastrin Evaluation:** Serum samples collected from all the study rats at necropsy were analyzed for gastrin levels using a radioimmunoassay. Reportedly serum gastrin increased in a MK-3118 dose-dependent manner with approximately 3 times, 5 times, and 40 times the serum gastrin levels in the LD, MD, and HD groups respectively compared to vehicle control values.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control, +: indicates increase in parameters compared to control.
*p ≤ 0.05; **p≤ 0.01; ***p ≤ 0.001 compared to vehicle control values.
APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TBIL: total bilirubin, BUN: blood urea nitrogen, GLUC: glucose, CHOL: cholesterol; TRIG: triglycerides, TPROT: total protein, ALB: albumin, CA: calcium

Study title/ number: One-Month Oral Toxicity Study in Dogs/ Study No.: TT #09-1091

- Beginning with the first week of dosing, mid- and high-dose animals experienced food/foamy emesis. Degeneration of the gastric mucosa in the stomach was observed in all high-dose males and females with slight severity and with less severity in two thirds of the males and females in the mid-dose group.
- Aspartate aminotransferase and alanine aminotransferase increased in a MK-3118 dose-dependent manner in the mid- and high-dose groups, but only to a moderate degree with increases of less than 100% in the mid-dose group and less than 200% in high-dose animals. A slight accumulation of dark green-brown pigment in canalicular spaces between hepatocytes is consistent with an early sign of cholestasis.
- The NOAEL was considered to be the low dose of 30 mg/kg/day which was associated with plasma C_{max} and $AUC_{0\text{-}24hr}$ values of 2.81 mcM (2.05 mcg/ml) and 32.9 mcM•hr (24.0 mcg•hr/ml) respectively.

Conducting laboratory and location: Merck Research Laboratories, PA, USA
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 30 (LD), 100 (MD) and 300 (HD) mg/kg/day administered once per day.
Route of administration:	Oral gavage
Formulation/Vehicle:	MK-3118 (ibrexafungerp, phosphate salt) was dissolved in 0.5% methylcellulose in deionized water.
Species/Strain:	Beagle dogs
Number/Sex/Group:	3/sex/group
Age:	33-37 weeks
Satellite groups/ unique design:	No satellite groups
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No unscheduled deaths occurred in the study.
Clinical Signs	MK-3118-related clinical signs observed in MD and HD animals beginning in the first week of dosing included: food/foamy emesis, unformed/liquid/ discolored/mucoid/scant feces, and pre and/or post-dose salivation. In the LD group, MK-3118-related effects were limited to unformed/liquid feces and occasional food/foamy emesis beginning in Week 1.
Body Weights	All the HD females and 2/3 HD males lost weight (0.5 to 0.6 kg) at the end of Week 4 compared to pre-dose values. A slight increase in mean weights (0.1 kg for females and 0.3 kg for males) for concurrent control animals was observed at the end of Week 4. Weight loss for HD animals began in Week 1. One MD male also lost approximately 1 kg relative to pretest values. The body weight changes at times correlated with emesis.
Ophthalmoscopy	No MK-3118-related changes in any ophthalmic findings were observed.
ECG	No changes in any ECG parameters were observed.
Hematology	The changes in hematology parameters shown below were not of clear toxicological relevance. **Week 5** HD females: -43% reticulocytes, -17% APTT, +54% fibrinogen MD females: -36% reticulocytes, -12% APTT HD males: -57% reticulocytes, +86% fibrinogen MD males: +30% fibrinogen
Clinical Chemistry	The changes in serum chemistry parameters shown below were not of sufficient magnitude to be considered toxicologically relevant. **Week 5** HD females: +164% AST, +100% ALT, -15% albumin, +11% globulin, -18% albumin/globulin ratio. MD females: +67% AST, +85% ALT HD males: +147% AST, +34% ALT, -18% albumin, +10% globulin, -24% albumin/globulin ratio. MD males: +79% AST, +51% ALT, -15% albumin, +10% globulin, -24% albumin/globulin ratio.
Urinalysis	No MK-3118-related changes in any urinalysis parameters were observed.
Gross Pathology	No MK-3118-related gross pathology findings were observed.

Organ Weights	No statistically significant changes in organ weights were considered related to MK-3118 administration.
Histopathology Adequate battery: Yes	**Stomach:** Dose-dependent degeneration of the gastric mucosa in the stomach occurred with slight severity in all HD males and females and with very slight severity in 2/3 males and 2/3 females in the MD group. **Liver:** Slight accumulation of dark green-brown pigment in canalicular spaces between hepatocytes primarily in the centrilobular region of the liver occurred in 1 HD male and 1 HD female. This finding may represent an early stage in the development of cholestasis. **Non-adverse Phospholipidosis:** Findings consistent with phospholipidosis including cell vacuolation and/or histiocytosis in multiple cells and organs occurred primarily in MD and HD animals of both sexes with severity increasing with dose up to moderate severity in HD animals. Affected cells and organs included: Kupffer cells, large intestine, gallbladder, lung, spleen, lymph node, and thymus.
[Other evaluations]	**Toxicokinetics:** see Section 5.4

LD: low dose; MD: mid dose; HD: high dose.
APTT: activated partial thromboplastin time; AST: aspartate aminotransferase, ALT: alanine aminotransferase
-: indicates reduction in parameters compared to control, +: indicates increase in parameters compared to control.
*p ≤ 0.05; **p≤ 0.01; ***p ≤ 0.001 compared to vehicle control values.

General toxicology; additional studies

Study title/ number: A 13-Week Study of SCY-078 by Oral Gavage in Rats with a 14-day Recovery Period./ Study No.: SCY078-TOX-011

- Histopathology findings occurred in a dose-dependent manner for incidence and severity in the stomach including mild glandular dilatation, decrease in parietal cells in males and females, eosinophilic cytoplasmic accumulations in chief cells in males and females, and single-cell necrosis in females. Mid- and high-dose males and females in all SCY-078 treatment groups were affected.
- The no-observed-adverse-effect level (NOAEL) in males was considered to be the low dose of 20 mg/kg/day corresponding to an AUC_{0-24} of 28,798 ng•hr/ml (39.6 mcM•hr). Although a NOAEL was not established in the females due to adverse stomach changes at all doses, in the low-dose females, the stomach observations either resolved or exhibited a decreased severity following the recovery period.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1, vehicle control), 20 (Group 2, LD), 40 (Group 3, MD) and 80 (Group 4, HD) SCY-078 citrate administered once per day.
Route of administration:	Oral gavage
Formulation/Vehicle:	SCY-078 (citrate salt form) was dissolved in 0.5% methylcellulose in deionized water.

Species/Strain:	Sprague Dawley Crl:CD(SD) rats
Number/Sex/Group:	15/sex/group for the Main Study and 5/sex/group for the Recovery Study
Age:	8 weeks
Satellite groups/ unique design:	Toxicokinetic animals: 3/sex for Group 1; 9/sex/group for Groups 2-4/ Male and female Sprague Dawley rats were administered vehicle or SCY-078 citrate once daily for 13 weeks by oral gavage. Main Study animals were euthanized and examined on Days 92/93 and Recovery animals were maintained for an additional 2 weeks before euthanasia on Day 106.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No unscheduled deaths occurred during the study.
Clinical Signs	No clinical signs were considered to be related to SCY-078 administration.
Body Weights	Statistically significant reductions in mean body weights occurred for HD males from Days 8 through 91 (-5.7% to -17.7%) and for MD males from Days 50 through 91 (-5.0% to -7.2%) compared to control values. The mean body weights for these 2 groups were closer to those of controls (-3.9% and -13.0% difference for the MD and HD groups, respectively) by the end of the recovery period. No significant reductions in body weights occurred for females treated with SCY-078 compared to control values.
Ophthalmoscopy	No changes in any ophthalmic assessments were considered related to SCY-078 administration.
Hematology	The changes in hematology parameters shown below were not considered to be of clear toxicological relevance. **Day 92/93 (End of Dosing)** HD males: +242% neutrophils*, -11% APTT***, +14% platelets, -20% reticulocytes**, +23% fibrinogen** MD males: -8% APTT***, -18% reticulocytes* HD females: +44% neutrophils, +12% platelets**, +12% fibrinogen **Day 106 (End of the Recovery Period)** At the end of the recovery period, platelet values were similar in all groups for both sexes and no significant differences from control values were observed for the SCY-078 treatment groups for any of the measured hematology and coagulation parameters.

Clinical Chemistry (serum values)

The changes in clinical chemistry parameters shown below were not considered to be of clear toxicological relevance.

Day 92/93 (End of Dosing)
HD males: +80% ALT***, +36% TBIL*, -25% GLUC***, -20% CHOL*, -37% TRIG**, -8% TPROT***, -14% ALB***, -3% CA*.
MD males: -16% GLUC**, -4% ALB*
HD females: +26% TBIL**

Day 106 (end of the Recovery Period)
At the end of the Recovery Period, no significant differences from control values were observed for the SCY-078 treatment groups for any of the measured hematology and coagulation parameters.

Urinalysis

No urinalysis parameters were altered in an SCY-078-related manner.

Gross Pathology

Gross pathology findings correlating with phospholipidosis were observed in several select organs in both sexes. Mesenteric lymph nodes were enlarged in 4/15 HD males. Lung and liver were discolored pale either focally in the lung (1/15 MD males; 4/15 HD males; 2/15 HD females) or more generally in liver (1/15 HD males). In recovery animals, pale lung foci were still observed in 3/5 HD males, 1/5 MD females, and 3/5 HD females.

Organ Weights

Organ weights in SCY-078 treatment groups were generally not significantly different than control values at the end of dosing and following the recovery period.

Histopathology
Adequate battery: Yes

Stomach: Histopathology findings occurred in a dose-dependent manner for incidence and severity in the stomach and included: mild glandular dilatation (in all groups with a higher incidence and/or severity in MD and HD males and females), apparent decrease in parietal cells in males and females (in LD females with a higher severity in MD and HD males and females), minimal to mild single-cell necrosis in females (3/15 HD females) (Table 5-9). These findings were considered related to SCY-078 administration and either clearly or potentially adverse. Following the recovery period, the incidence and severity of the stomach findings was decreased but not completely resolved in MD and HD animals and eosinophilic accumulation in chief cells remained with minimal severity in 4/5 LD females.

Table 5-9: Stomach Histopathology Findings at the End of Dosing in the 13-Week Toxicology Study in Rats. (Table from the study report)

	Males				Females			
Group	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Dose (mg/kg/day)	**0**	**20**	**40**	**80**	**0**	**20**	**40**	**80**
No. Animals Examined	**15**	**15**	**15**	**15**	**15**	**15**	**15**	**15**
Stomach (No. Examined)	**(15)**	**(15)**	**(15)**	**(15)**	**(15)**	**(15)**	**(15)**	**(15)**
Dilatation, glandular	(3)[a]	(4)	(7)	(14)	(1)	(2)	(14)	(15)
Minimal	3	4	7	13	1	2	12	12
Mild	0	0	0	1	0	0	2	3
Decreased cellularity; parietal cell	(0)	(0)	(14)	(14)	(0)	(11)	(13)	(15)
Minimal	0	0	7	7	0	9	8	0
Mild	0	0	7	7	0	2	5	7
Moderate	0	0	0	0	0	0	0	7
Marked	0	0	0	0	0	0	0	1
Accumulation; eosinophilic, chief cell	(0)	(0)	(4)	(14)	(0)	(8)	(11)	(15)
Minimal	0	0	4	13	0	8	9	5
Mild	0	0	0	1	0	0	2	7
Moderate	0	0	0	0	0	0	0	3
Single cell necrosis; epithelial, glandular	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(3)
Minimal	0	0	0	0	0	0	0	1
Mild	0	0	0	0	0	0	0	2

[a] Number in parentheses represent the number of animals with the finding

	Abscess Formation: In HD males, mild to severe abscesses were microscopically observed in the spleen (2/15 HD males), mesenteric lymph node (5/15 HD males) and adrenal gland (1/15 HD males). The abscesses in the mesenteric lymph node were accompanied by accumulations of foamy macrophages. The abscesses appear to be related to SCY-078 administration, but the mechanism underlying their formation is not clear. One possible mechanism put forth in the study report is that the abscesses may have occurred secondary to altered macrophage function. No abscesses remained in any tissues after the recovery period. **Non-adverse Phospholipidosis:** Accumulations of histiocytes with foamy cytoplasms in multiple tissues occurred in a dose-dependent manner for incidence and severity and were interpreted as being consistent with phospholipidosis. Affected organs included the lung (accumulations of histiocytes in LD, MD, and HD males and LD, MD, and HD females), spleen (histiocytosis in MD and HD males and HD females), small intestine (histiocytes in MD and HD males and females) and mesenteric lymph node (accumulations of histiocytes in LD, MD, and HD males and MD and HD females).
[Other evaluations]	**Toxicokinetics:** see Section 5.4

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control, +: indicates increase in parameters compared to control.
*p ≤ 0.05; **p≤ 0.01; ***p ≤ 0.001 compared to vehicle control values.
APTT: activate partial thromboplastin time, ALT: alanine aminotransferase, TBIL: total bilirubin, GLUC: glucose, CHOL: cholesterol, TRIG: triglycerides, TPROT: total protein, ALB: albumin, and CA: calcium

Study title/ number: A 13-Week Study of SCY-078 by Oral Gavage in Dogs with a 14-day Recovery Period./ Study No.: SCY078-TOX-012

- Administration of SCY-078 citrate by once daily oral gavage for 13 weeks was well tolerated in dogs at dose levels of 15, 30, and 60 mg/kg/day. There were no toxicologically relevant changes in body weights, body weight gains, food consumption, ophthalmology, electrocardiography, clinical pathology parameters, or gross necropsy findings.
- Microscopic changes in the lung and the lymphoid tissues of both sexes were consistent with phospholipidosis and considered to be non-adverse.
- Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be the high dose of 60 mg/kg/day which corresponded to plasma AUC_{0-24} values of 39,779 ng•hr/ml (54.7 mcM•hr) for males and 27,413 ng•hr/ml (37.7 mcM•hr) for females.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1, vehicle control), 15 (Group 2 LD), 30 (Group 3, MD), and 60 (Group 4, HD) mg/kg/day administered once per day.
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose in deionized water

Species/Strain:	Beagle dogs
Number/Sex/Group:	Main Study: 4/sex/group; Recovery Study: 2/sex/group
Age:	6-months
Satellite groups/ unique design:	Separate toxicokinetic animals were not included./ Male and female Beagle dogs were administered vehicle or SCY-078 by oral gavage once daily from Day 1 to Day 91/92 before euthanasia on Day 92/93. Recovery animals were maintained without dosing for an additional 2 weeks before euthanasia on Day 106.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One HD male was euthanized early on Day 88 following dosing due to an apparent gavage error.
Clinical Signs	HD animals had abnormal feces (92 and 117 observations for males and females respectively) and emesis (72 and 62 observations for males and females respectively). Fewer of the same clinical signs were observed in MD animals with 81 male and 88 female observations of abnormal feces and 5 male and 29 female observations of emesis. LD and control animals had similar incidences of abnormal feces (33 male and 32 female observations in the LD group compared to 36 male and 27 female observations in the control group) and emesis (7 male and 12 female observations in the LD group compared to 3 male and 13 female observations in the control group).
Body Weights	No significant changes in body weight or body weight gains were observed in any of the SCY-078-treatment groups compared to control values. A nonsignificant dose-dependent trend toward reduced body weight gain in females occurred with body weight gains on Day 91 of 1.6 kg, 1.4 kg, 1.0 kg, and 1.1 kg for females in the control, LD, MD, and HD groups.
Ophthalmoscopy	No ophthalmic findings were considered related to SCY-078 administration.
ECG	No changes in ECG measurements in the last week of dosing were considered related to SCY-078 administration. Because no ECG changes occurred during the Main Study, ECG assessments were not performed in Recovery animals.

Hematology	The changes in hematology parameters shown below were not considered to be of clear toxicological relevance. **Day 92 (end of dosing)** LD males: -36% reticulocytes* MD males: -53% reticulocytes***, -25% WBC* -58% basophils*, -13% HGB, -13% HCT. HD males: -56% reticulocytes***, -18% WBC*, LD females: -44% reticulocytes*, -18% WBC*, -22% LYMPH MD females: -39% reticulocytes, -16% WBC*, -24% LYMPH HD females: -32% reticulocytes, -17% WBC*, All the reduced hematology parameters still fell within the historical control range. **Day 106 (end of the Recovery Period)** At the end of the recovery period, reticulocytes were still reduced in MD and HD females by about the same percentages as on Day 92. Values were similar in all groups for both sexes with no substantial differences from control values for the other measured hematology and coagulation parameters.
Clinical Chemistry	The changes in serum chemistry parameters shown below were not considered to be of clear toxicological relevance. **Day 92 (end of dosing)** MD males: +35% CHOL*, +25% TRIG* HD males: +42% CHOL** **Day 106 (end of the Recovery Period)** Serum cholesterol remained non-significantly increased by 15%-20% at the end of the recovery period in MD and HD males compared to control values.
Urinalysis	No SCY-078-related changes in any urinalysis parameters were observed.
Gross Pathology	At the end of the treatment period on Day 92/93, no SCY-078-related gross pathological findings were observed. At the end of the 2-week recovery period (Day 106), gross findings were noted in the lung (foci; pale) in 1 female each in the MD and HD groups, which correlated microscopically with alveolar accumulation of foamy histiocytes observed microscopically in the Main Study females.
Organ Weights	No SCY-078-related organ weight changes were noted at the Main Study necropsy on Day 92/93 or at the Recovery necropsy on Day 106.
Histopathology Adequate battery: Yes	SCY-078-related histiocytosis occurred in a dose-dependent manner for incidence and severity in the lung and the lymphoid tissues [mandibular and mesenteric lymph nodes, splenic white pulp, and Gut Associated Lymphoid Tissue (GALT)] of both sexes. The changes were considered non-adverse and related to phospholipidosis in the affected organs.
[Other evaluations]	**Toxicokinetics:** See Section 5.4

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control, +: indicates increase in parameters compared to control.
*p ≤ 0.05; **p≤ 0.01; ***p ≤ 0.001 compared to vehicle control values.
WBC: white blood cell count; HGB: hemoglobin; LYMPH: lymphocyte count; CHOL: cholesterol; TRIG: triglycerides

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Microbial Mutagenesis Assay/TT #09-8034

Key Study Findings:

- MK-3118 was considered negative for mutagenicity. None of the tested concentrations produced a 2-fold or greater increase in revertants relative to control values with and without the addition of rat S9.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains: TA 1535, TA97a, TA98, and TA100; *Escherichia coli* strain WP2 uvrA pKM101
Study is valid: Yes

Study title/ number: MK-3118: Microbial Mutagenesis Pre-Incubation Assay Using Human S-9./TT #09-8040
Key Study Findings:

- MK-3118 was considered negative for mutagenicity in all the tested strains of bacteria with and without the addition of human S9. None of the tested concentrations produced a 2-fold or greater increase in revertants relative to control values.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains: TA 1535, TA97a, TA98, and TA100; *Escherichia coli* strain WP2 uvrA pKM101
Study is valid: Yes

In Vitro Assays in Mammalian Cells
Study title/ number: MK-3118: Assay for Chromosomal Aberrations in Vitro, in Chinese Hamster Ovary Cells./ TT #09-8632 and TT #09-8633
Key Study Findings:

- None of the scored concentrations of MK-3118 produced increases in the percent of cells with chromosomal aberrations above the concurrent solvent control values with and without S9 activation in an in vitro chromosome aberration assay in CHO cells.

GLP compliance: Yes
Test system: Chinese hamster ovary cells
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: MK-3118: Assay for Micronucleus Induction in Rat Bone Marrow from a 1-Month Oral Toxicity Study/ TT #09-8731
Key Study Findings:

- Oral gavage doses of 40, 80, and 200 mg/kg/day MK-3118 for 30 days were not associated with an increase in the micronucleated polychromatic erythrocytes in bone marrow cells compared to vehicle control values.

GLP compliance: Yes
Test system: Bone marrow cells from the humerus bones from treated Han Wistar rats.

Study is valid: Yes

5.5.3. Carcinogenicity

No carcinogenicity studies have been conducted for ibrexafungerp.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Study of Fertility and Early Embryonic Development to Implantation of SCY-078 Administered by Oral (Gavage) in Rat/ SCY078-TOX-025

Key Study Findings

- Both male and female rats exhibited significant reductions in body weights of less than 10% in the high-dose group receiving 80 mg/kg and significant reductions in body weight gains.
- All mating and fertility parameters for males were not affected by administration of SCY-078. In addition, SCY-078 did not affect the motility of sperm in the vas deferens or sperm density in the cauda epididymis.
- All mating and fertility parameters were not affected by administration of SCY-078 in females.

Conducting laboratory and location	(b) (4)
GLP compliance: Yes	

Methods

Dose and frequency of dosing:	0, 10, 20, 40, and 80 mg/kg/day SCY-078 (citrate salt)
Route of administration:	Oral gavage
Formulation/Vehicle:	SCY-078 citrate salt was dissolved in 0.5% methylcellulose in deionized water
Species/Strain:	Han Wistar rats -Crl: WI(Han)
Number/Sex/Group:	22/sex/group
Satellite groups:	None
Study design:	Males were administered SCY-078 or vehicle by oral gavage once daily beginning 28 days before cohabitation, during cohabitation, and continuing through the day before euthanasia on Day 64. Females were administered SCY-078 or vehicle by oral gavage once daily beginning 15 days before mating, during mating, and continuing until gestation day (GD) 7. Females were subsequently euthanized on GD 13. Treated males were mated with treated females, and males administered vehicle were mated with females administered vehicle.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	All males and females survived until their scheduled euthanasia.
Clinical Signs	**Males:** Clinical signs in HD male rats (80 mg/kg/day) included rales (61 observations in 7/22 rats), mild dehydration (39 observations in 5/22 rats), excess salivation (6 observations in 4/22 rats), and chromorhinorrhea (5 total observations in 3/22 rats). Also, hunched posture and urine-stained abdominal fur occurred in individual HD males in conjunction with excess salivation or rales and dehydration. In most cases, the signs occurred after 3 weeks of dosing. No clinical signs were observed in control males or males administered 40 mg/kg/day and a low incidence of rales and dehydration (3 or less observations) was observed in only 1/22 males in the 10 and 20 mg/kg/day groups. **Females:** HD females (80 mg/kg/day) demonstrated clinical signs including mild dehydration (32 total observations in 4/22 females), hunched posture (11 total observations in 4/22 females) and rales (9 observations in 3/22 females) during the premating period. The observations first occurred during the Day 4 to Day 10 interval.
Body Weights	**Males:** Mean body weights were statistically significantly decreased in the 40 and 80 mg/kg/day dose groups for multiple measurement intervals between Days 4 and 64. However, body weights were not decreased more than 10% and ranged from 91% to 97% of control values at each interval for the 80 mg/kg/day group. In the 40 mg/kg/day dose group, body weights were reduced by 4% to 6% compared to control values for all the measurement intervals between Day 11 and Day 64. Mean body weight gain was significantly reduced for the 40 and 80 mg/kg/day groups during multiple intervals between Days 4 and 64. At 40 mg/kg/day, significant reductions in mean body weight gain were noted during the 1-month premating period for all the measurement intervals except the Day 15 to 18 interval until Day 22 with reductions in body weight gain ranging from 30% to 55% relative to control values. Mean body weight gains for the entire pre-mating period (Days 1 to 28) and the entire study period (Days 1 to 64) were significantly reduced by 27% and 19%, respectively, for the 40 mg/kg/day group compared to control values. In the 80 mg/kg/day group, mean body weight gain was reduced during the premating period for the Day 1 to 4 interval (significant mean body weight loss of 0.4 g compared to a body weight gain of +5.6 g in controls), the Day 4 to 8 interval (74% reduction compared to the mean control value), and the Day 18 to 22 interval (77% reduction compared to the mean control value). Mean body weight gain was reduced 43% and 32% relative to the mean body weight gain for the control group for the entire pre-mating period (Days 1 to 28) and entire study period (Days 1 to 64), respectively. **Females** **Premating Period:** Mean maternal body weights were slightly but statistically significantly reduced in the 80 mg/kg/day group on Days 4 (-5%), 8 (-7%), 11 (-5%), and 15 (-5%) of the premating period. A significant but minimal body

	weight reduction was noted on Day 8 in the 40 mg/kg/day dose group (-3% compared to control values). Reduced mean body weight gains occurred during the first week of dose administration during the premating period in all the SCY-078 dose groups. Reductions in mean body weight gain were noted for the Day 1 to Day 4 interval in the 10 (body weight gain that was 29% of the mean control value), 20 (29% of controls), and 40 (34% of controls) mg/kg/day dose groups and body weight loss occurred at 80 mg/kg/day (mean value of -5.5 g compared to control mean value of +3.5 g) with significant changes observed in the 10, 20, and 80 mg/kg/day dose groups. Dose-dependent reductions in mean body weight gains were noted at dose levels of 10, 20, 40, and 80 mg/kg/day on the Day 4 to 8 interval (94%, 62%, 58%, and 47% of controls, respectively) and the reduction was significant in the 80 mg/kg/day group. Mean body weight gains for the overall pre-mating interval (Days 1 to 15) were 70%, 67%, 78%, and 35% of controls in the 10, 20, 40, and 80 mg/kg/day dose groups, respectively, with significant reductions in the 20 and 80 mg/kg/day groups compared to control values. **Gestation Period:** Mean body weights were slightly but statistically significantly reduced by 6% to 7% in the 80 mg/kg/day group compared to control values on gestation days (GDs) 0, 3, 7, and also on GD 10 after dosing ended on GD 7. Maternal body weight gains were reduced during dose administration from GD 0 to GD 7 in the 80 mg/kg/day group compared to control values, but the reductions were not statistically significant. Body weight gains in the 80 mg/kg/day group were reduced by 7% for the GD 0 to GD 3 interval, 27% for the GD 3 to GD 7 interval, and 17% for the GD 0 to GD 7 interval compared to control values. After the end of dose administration on GD 7, animals in the 80 mg/kg/day group had increased body weight gain compared to control values with statistically significant increases for the GD 7 to GD 10 interval (+29% compared to control values) and the GD 7 to GD 13 interval (+16% compared to control values).
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]*	**Males:** All mating and fertility parameters including the number of days for mating, the number of male rats that mated, the fertility index (number of pregnancies/number of rats that mated), and the number of male rats that mated in the first week were similar in the control and SCY-078-treatment groups. Sperm evaluations were conducted for all the male rats. Motility of sperm in vas deferens was similar in control and treatment groups (mean values of 86% to 89% percent motile sperm in all groups). The density of sperm in cauda epididymis was not decreased in any of the SCY-078 treatment groups compared to control values. **Females:** No SCY-078-related effects on the days needed for mating (2.5 to 3.2 days), mating index (100% in all groups) or fertility index (86.4 to 100%) were observed at any dose. No SCY-078-related gross pathology findings were observed. Pregnancy was confirmed in 100.0%, 95.4%, 86.4%, 100.0%, and 95.4% females in the 0, 10, 20, 40, and 80 mg/kg/day groups, respectively. The litter averages for corpora lutea, implantation, preimplantation loss, viable and nonviable embryos, and postimplantation

	loss were comparable among all 5 study groups. No litters consisted only of nonviable embryos. All placentae appeared normal for all groups. The mean number of estrous stages per 14 days was non-significantly reduced in the 80 mg/kg/day group (3.23) by 9% compared to the mean control value (3.55). However, the observed number of estrous stages in both groups were within the historical control range (3.1 to 3.7 estrous stages/14 days for 203 female rats in 10 studies). One female in the 40 mg/kg group and two females in the 80 mg/kg/day group exhibited six or more consecutive days of diestrus. The incidence of females exhibiting six or more consecutive days of diestrus was above the historical control range (0 to 0 % for data derived from 9 studies) for the 40 and 80 mg/kg/day groups, but this pattern was not associated with changes in the mating or fertility indexes for the affected groups.

LD: low dose; MD: mid dose; HD: high dose

Embryo-Fetal Development

Study title/ number: An Embryo-Fetal Development Study of SCY-078 by Oral (Gavage) in Rats/ SCY078-TOX-023

Key Study Findings

- Maternal toxicity was minimal consisting of decreased body weight gain for high-dose dams in the first measurement interval during dosing (GD 6 to GD 9) but not thereafter during the dosing period or for the entire study period.
- No SCY-078-related changes in Caesarean section data including fetal body weights were observed and no SCY-078-related fetal malformations were observed.
- The NOAEL value for maternal and fetal toxicity, the high-dose of 50 mg/kg/day SCY-078, was associated with maternal plasma C_{max} and $AUC_{(0-t)}$ values of 2630 ng/ml and 50900 ng•hr/ml respectively on the last day of dosing, GD 17.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 10 (Group 2), 20 (Group 3), 35 (Group 4), and 50 mg/kg/day (Group 5) administered once daily inclusive from GD 6 to GD 17.
Route of administration:	Oral gavage
Formulation/Vehicle:	The citrate salt form of SCY-078 was dissolved in the vehicle, 0.5% methylcellulose in deionized water.
Species/Strain:	Wistar Han rats – Crl:WI(Han)
Number/Sex/Group:	25 pregnant females per group
Satellite groups:	Toxicokinetic females: 3 in Group 1 and 6/group in Groups 2-5.

Study design:	Pregnant female rats were administered vehicle or SCY-078 (10, 20, 35, and 50 mg/kg/day) by oral gavage once daily on GDs 6 through 17 then euthanized on GD 21. Females were evaluated for viability, clinical signs, body weights, food consumption, gross pathology, and Caesarean section findings. Also, blood samples were collected for toxicokinetic analysis.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	All females survived until the scheduled euthanasia on GD 21.
Clinical Signs	Clinical signs potentially related to SCY-078 administration included red mouth discharge on GD 6 in single rats in the 35 mg/kg/day group, and in the 50 mg/kg/day group, red mouth discharge on GD 7 in single rats, and abnormal breathing sounds (GDs 14 to 21) in three rats for up to 6 days.
Body Weights	Mean body weights were not significantly reduced in any of the treatment groups compared to control values during any of the study intervals. Mean maternal body weight gains were reduced at the beginning of the dose period (GDs 6 to 9) in the 20 (14% reduction compared to controls), 35 (26% reduction compared to controls), and 50 (45% reduction compared to controls) mg/kg/day groups, and the reduction was statistically significant in the HD group. However, body weight gains were similar in all groups beginning on GD 9 and body weight gains for the SCY-078 treatment groups were not reduced relative to vehicle control values for the whole dosing period (GDs 6 to 18), in the postdose period (GD 18-21), or for the whole study period (GD 6 to 21).
Necropsy findings Cesarean Section Data	There were no SCY-078-related effects on the mean number of corpora lutea, implantation sites, percent pre-implantation loss, percent post-implantation loss, live fetuses, early resorptions, percent male fetuses, or mean fetal body weights at any dose level. There were no late resorptions or dead fetuses and no litters that consisted of only resorbed conceptuses. All placentae appeared normal.
Necropsy findings Offspring	**External Anomalies:** No external malformations or variations were observed in any group. **Visceral Anomalies:** A low number of visceral malformations were observed in fetuses in the HD group but not in the other SCY-078 treatment groups or the control group. However, all the fetuses afflicted with each category of malformation occurred in the same litter within the HD group. Four fetuses in HD Litter #1809 demonstrated enlarged hearts, 1 fetus in HD Litter #1817 had a small left eye and an absent right eye and another fetus also in Litter #1817 had an absent right eye. In the historical control data collected from control groups in 15 studies conducted from 2012-2019, no data were available for two of the fetal malformations observed in the present study, enlarged heart and absent eye. However, because the visceral malformations that were observed in

	the present study occurred only in single HD litters, the malformations were not considered to be related to SCY-078 administration. **Skeletal Anomalies:** A single fetus in the 20 mg/kg/day group had a bent humerus, radius, ulna, and femur. The historical control data collected from 26 studies conducted from 2012 to 2019, did not include any of the skeletal malformations observed in the present study. However, because the skeletal malformations occurred in a single fetus and not in an SCY-078 dose-related manner, the malformations were not considered to be related to SCY-078 administration.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: An Embryo-Fetal Development Study of SCY-078 by Oral (Stomach Tube) in Rabbits/ Study No.: SCY078-TOX-024

Key Study Findings

- In the mid-dose group, fetal malformations including absent ear pinna, general body craniorachischisis, thoracogastroschisis, trunk kyphosis, absent hindpaw, and forelimb phocomelia occurred in a single fetus but not in fetuses in the vehicle control group or in comparable historical control data.
- Malformations including absent hindpaw and anencephaly occurred with an increased litter incidence in the high-dose group compared to the vehicle control group and historical control data. Other malformations that occurred in single fetuses but not in the vehicle control group or in comparable historical control data included absent ear pinna, forelimb phocomelia, thoracogastroschisis, and absent thyroid gland.
- The NOAEL value for maternal toxicity is considered to be the high dose of 50 mg/kg/day (approximately equal to 13.5 times the expected clinical exposure in fed patients based on AUC comparison). The NOAEL for fetal toxicity is considered to be the low dose of 10 mg/kg/day (approximately equal to 1.8 times the expected clinical exposure based on AUC comparison).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10 (LD), 25 (MD), and 50 (HD) mg/kg/day SCY-078 (citrate salt form)
Route of administration:	Oral gavage via stomach tube
Formulation/Vehicle:	SCY-078 citrate salt was dissolved in 0.5% methylcellulose (400 cps) in deionized water.
Species/Strain:	Dutch Belted rabbits - Haz(DB)SPF
Number/Sex/Group:	20 pregnant females per group
Satellite groups:	Toxicokinetic animals: 3 pregnant females in in the vehicle control group, and 6 pregnant females per group in the LD, MD, and HD groups.

Study design:	Pregnant rabbits were administered vehicle or SCY-078 from GD 7 to GD 19 before euthanasia and caesarean section analysis on GD 29. All animals were monitored for viability, clinical signs, body weights, body weight changes, food consumption, ovarian and uterine findings, and gross pathology. In addition, maternal blood samples were collected for toxicokinetic analysis on GDs 7 and 19.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	All Main Study and toxicokinetic females survived until the scheduled euthanasia except for one control female found dead on GD 20 which apparently died from an esophageal perforation caused by an intubation error.
Clinical Signs	No SCY-078-related clinical signs were observed.
Body Weights	Maternal body weights were not changed in any of the SCY-078 dose groups compared to control values, but mean body weight gains were reduced for the MD and HD groups during most of the dosing period. In the HD group for the interval of GD 7 to 10, there was a statistically significant mean maternal body weight loss (-19.15 g) compared to a body weight gain of +15.12 g in controls. Thereafter, mean maternal body weight gains were nonsignificantly reduced in the HD group for the intervals of GD 10 to 13 (78% of the mean weight gain for control females) and GD 13 to 16 (82% of the control weight gain). Subsequently, there was an increase in mean maternal body weight gain in the HD group for the interval of GD 16 to 20 (183% of the control weight gain) with weight gain values similar to control values after GD 20. In the MD group, mean maternal body weight gain was nonsignificantly reduced for the intervals of GD 7 to 10 (29% of the mean weight gain for control females), GD 10 to 13 (66% of control weight gain), and GD 13 to 16 (93% of control weight gain). Similar to the pattern that occurred in the HD group, there was an increase in mean maternal body weight gain for the interval of GD 16 to 20 (176% of control weight gain), followed by weight gain values similar to the control group after GD 20. Mean body weight gains were, respectively, 97% and 79% of the mean control weight gain for the MD and HD groups for the entire dosing period (GD 7 to GD 20), 87% and 86% of mean control values for the post-dose period (GD 20 to GD 29) and 91% and 83% of mean control values for the entire study period (GD 7 to GD 29).
Necropsy findings Cesarean Section Data	Pregnancy was confirmed in 19, 20, 20, and 20 females in the control, LD, MD, and HD groups respectively. There were no statistically significant SCY-078-related effects on any ovarian or uterine parameters in any of the SCY-078 dose groups. The mean number of corpora lutea, implantation sites, percent pre-implantation loss, percent post-implantation loss, live and dead fetuses, early and late resorptions and percent male fetuses/litter were not significantly different in any of the SCY-078 treatment groups compared to

	control values. The mean total number of resorptions in the LD group (0.6) was significantly increased compared to control values (0.1), but the increase was not dose-dependent and not considered to be related to SCY-078 administration. Mean fetal weights were reduced relative to control values by 7% in HD male fetuses and 8% in HD female fetuses, but the differences were not statistically significant.
Necropsy findings Offspring	**External anomalies:** The fetal and litter incidences of external malformations were increased in the HD group (9/140 fetuses, 3/20 litters) compared to incidences in the MD (2/147 fetuses, 2/20 litters), LD (2/144 fetuses, 2/20 litters) and vehicle control (1/129 fetuses, 1/18 litters) groups. Rare external malformations were observed primarily in one MD fetus and two HD fetuses in two litters. Fetal external malformations in the MD and HD groups included general body craniorachischisis (occurred in one MD fetus), trunk kyphosis (occurred in one MD fetus), exencephaly (occurred in one HD fetus), thoracogastroschisis (occurred in one MD fetus and one HD fetus), forelimb phocomelia (occurred in one MD fetus and one HD fetus), absent ear pinna (occurred in one MD and one HD fetus), absent hindpaw (occurred in one MD fetus and two HD fetuses in two litters) and anencephaly (occurred in two HD fetuses in two litters). None of these malformations occurred in the vehicle control group or in the historical control data. In contrast, the malformations that were observed in single fetuses in the vehicle control group, including acephalostomia, and meningocele all occurred within the range of fetal and litter incidences in the historical control data. The fetal and litter incidences of external variations were similar in the control and SCY-078 treatment groups. **Visceral Anomalies:** The fetal and litter incidences of fetal visceral malformations were increased in the HD group (4/140 fetuses, 4/20 litters) compared to incidences in the MD (2/147 fetuses, 2/20 litters), LD (3/144 fetuses, 3/20 litters) and vehicle control (2/129 fetuses, 2/18 litters) groups. Fetal visceral malformations in the MD and HD groups that did not occur in the vehicle control group or in historical control data included multiple malpositioned organs (occurred in one MD fetus and one HD fetus) and absent thyroid gland (occurred in one HD fetus). In contrast, all the fetal visceral malformations observed in single fetuses in the vehicle control group (absent cerebral hemisphere, absent eye, absent kidney) occurred within the range of fetal and litter incidences in the historical control data. The fetal and litter incidences of visceral variations were similar in the control and SCY-078 treatment groups. **Skeletal Anomalies:** The fetal and litter incidences of skeletal malformations were increased in the HD group (10/140 fetuses, 3/20 litters) compared to incidences in the MD (1/147 fetuses, 1/20 litters), LD (0/144 fetuses, 0/20 litters) and vehicle control (2/129 fetuses, 1/18 litters) groups. The fetal skeletal malformations that occurred in the MD and HD groups, but not in the vehicle control group or in the historical control data included multiple absent skull bones that occurred in one MD fetus and in two HD fetuses in two litters. In contrast, all the fetal skeletal malformations that occurred in the vehicle control group occurred in single fetuses within the range of fetal and litter incidences in the historical control data. The fetal and litter incidences of skeletal variations in the HD group (34/140 fetuses, 12/20 litters) were the same or slightly increased relative to the incidences in the MD (21/147 fetuses, 12/20 litters), LD (22/144 fetuses, 12/20 litters) and vehicle control (15/129 fetuses, 9/18 litters) groups.

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: A Developmental and Perinatal/Postnatal Reproduction Study of SCY-078 by Oral Gavage in Rats, Including a Postnatal Behavioral/Functional Evaluation/ SCY078-TOX-029

Key Study Findings

- Limited maternal toxicity was characterized by minimal reductions in body weights and/or body weight gains and reduced food consumption during the gestation and lactation periods.
- F1 offspring did not experience SCY-078-related changes in viability, neurological development or reproductive capacity.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (Group 1), 10 (Group 2), 20 (Group 3), 35 (Group 4), and 50 mg/kg/day (Group 5) SCY-078 citrate salt was administered to pregnant rats once per day from GD 6 to LD 20 (rats that littered) or GD 24 (rats that did not litter).
Route of administration:	Oral gavage
Formulation/Vehicle:	SCY-078 (citrate salt form) was dissolved in 0.5% methylcellulose in deionized water.
Species/Strain:	Wistar Han (Crl:WI Han) rats
Number/Sex/Group:	22 females/group
Satellite groups:	None
Study design:	Pregnant female rats were administered SCY-078 or the vehicle (0.5% methylcellulose) once daily by oral gavage from gestation day (GD) 6 through lactation day (LD) 20 (rats that littered) or GD 24 (rats that did not litter). The parental-generation (F0) females were euthanized on LD 21, or, for those that did not litter, on GD 25. First-generation (F1) offspring were not directly administered SCY-078 or vehicle. All F1 offspring were weaned on LD 21, and after weaning, 22 male and 22 female offspring in each group were chosen for further evaluation of physical and neurological development and beginning on postnatal day (PND) 90, mating and an assessment of reproductive capacity. The F1 offspring that were not selected for

	further evaluation were euthanized on LD 21. F1 males that were included for mating as part of the evaluation of reproductive capacity were euthanized after the 2-week mating period, and F1 females that became pregnant were euthanized on GD 13.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	Body Weights and Body Weighty Gains **Gestation Period:** Mean body weights were not reduced at the end of gestation for any of the SCY-078 treatment groups. Body weight gains were statistically significantly reduced from GD 6 to 9 in the 35 and 50 mg/kg/day groups compared to control values, but significant reductions did not occur for later intervals during gestation. **Lactation Period:** Minimal reductions in mean body weights ranging from 3.8% to 5.7% were observed in the 35 and 50 mg/kg/day dose groups on LDs 10, 12, 14, 15, and 16 (50 mg/kg/day group only). Mean body weight gains were significantly reduced without dose dependency by 40% to 59% at all SCY-078 dose levels on LDs 7 to 10. Body weight gains for the entire lactation period (LD 1 to LD 21) was similar for all groups. Food Consumption **Gestation Period:** Dose-dependent, statistically significant reductions in food consumption values occurred at the beginning of the gestation period (GD 6 to 9) in the 20, 35 and 50 mg/kg/day dose groups. Average food consumption at 50 mg/kg/day continued to be significantly reduced compared to control values until GD 18, and food consumption in the 35 mg/kg/day dose group was significantly reduced from GD 12 to GD 15. Mean food consumption for the entire gestation period (GD 6 to 18) was significantly reduced in the 35 mg/kg/day (94.1% of control values) and 50 mg/kg/day (90.6% of control values) groups. Food consumption values were comparable among all five study groups from GD 18 to 21. **Lactation Period:** Food consumption during the lactation period was similar for the control and treatment groups. Uterine Content: Pregnancy occurred in 22, 21, 22, 21, and 22 out of 22 mated female rats in the 0, 10, 20, 35, and 50 mg/kg/day dose groups, respectively. All pregnant dams delivered litters. Values for the numbers of dams delivering litters, the duration of gestation, mean number of implantation sites per delivered litter, the gestation index (number of dams with one or more liveborn pups/number of pregnant rats), the numbers of dams with stillborn pups, the number of dams with full litter loss, litter sizes, and the percent of male offspring per total offspring per litter were similar for the control group and the four SCY-078 dose groups.
F1 Generation	Survival and Clinical Signs: The viability index for LD 4 compared to LD 1 and for LD 21 compared to LD 4 was similar in all groups. None of the clinical signs observed in F1 offspring were considered to be related to SCY-078 administration. Body Weights: Changes in mean body weight and body weight gains did not occur in a SCY-078 dose-related manner or consistently for both sexes. Food Consumption: Food consumption was similar in all groups during the mating and gestation periods for F1 offspring.

	Physical Development: No effects on the sexual maturation of male and female F1 offspring was observed. The mean day for preputial separation (mean values of approximately 44 days for all groups) and vaginal patency (mean values of approximately 30 days for all groups) were comparable for the control and treatment groups. ***Note:*** *Other than neurological assessments, only parameters of reproductive development were assessed. Other indicators of physical development, including surface righting, air righting, time to incisor eruption, pinna unfolding, and eye opening, were not assessed.* Neurological Assessments: There were no biologically relevant differences in the SCY-078 treatment groups compared to control values for learning, short-term retention, long-term retention, or response inhibition in Passive Avoidance assessments. Similarly, no biologically relevant changes related to SCY-078 administration were observed for learning, short-term retention, long-term retention, or response inhibition in Morris Watermaze assessments. Reproduction: The fertility index for male F1 offspring was between 95% and 100% in all groups. Ovarian and uterine observations for F1 offspring were based on 20, 21, 21, 21, and 21 pregnant rats with one or more live fetuses in the 0, 10, 20, 35 and 50 mg/kg/day dose groups, respectively. No ovarian, uterine, or litter parameters in F1 offspring were affected by maternal F0 dosages of SCY-078 as high as 50 mg/kg/day. In female F1 offspring, the litter averages for corpora lutea, implantations, percent preimplantation loss, viable and nonviable embryos, and percent postimplantation loss were comparable for the control group and the four treatment groups. No F1-generation dam had a litter consisting of only nonviable embryos, and all placenta appeared normal.
F2 Generation	No assessments of F2-generation offspring were conducted in this study after Caesarean section delivery of F2 offspring on GD 13. The mean number of viable F2 embryos was similar in all groups after delivery on GD 13.

5.5.5. Other Toxicology Studies

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: *Salmonella Typhimurium* Bacterial Reverse Mutation Assay (Ames Test), Liquids or Soluble Chemicals GLP Report/ Study No.: 904463-S01

Key Study Findings:

- Two ibrexafungerp impurities, [redacted] (b) (4) impurity, were assessed for genetic toxicity in an Ames plate-incorporation assay with and without S9 activation over a range of concentrations [redacted] (b) (4) for both impurities.
- No cytotoxicity or precipitation was observed with either impurity. Revertant values for both impurities were similar to those for solvent controls for all tester strains with and without S9 activation. [redacted] (b) (4) produced at least a 500% increase in the number of revertants compared to solvent control values for each tester strain with and without S9 activation.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains: TA97a, TA98, TA100, TA102 and TA1535.
Study is valid: Yes

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Infectious Disease Pharmacology and Division of Pharmacometrics) reviewed the information contained in NDA 214900. See Table 6-1 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 6-1. Summary of OCP Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness of ibrexafungerp in patients with VVC was provided by two Phase 3 studies (VANISH -303 and VANISH -306). Supportive evidence of effectiveness was provided by two Phase 2 trials: a proof of concept trial (SCY-078-203) and a dose finding trial (SCY-078-204) and animal studies demonstrating a 9-fold higher exposure in vaginal tissue than in blood (SCY078-ADME-035).
General dosing instructions	The recommended dosing regimen is 300 mg (two 150 mg tablets) approximately 12 hours apart (i.e., in the morning and in the evening) for one day with or without food for a total treatment dosage of 600 mg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	When ibrexafungerp is concomitantly used with a strong CYP3A inhibitor, the dose should be reduced to 150 mg (one 150 mg tablet) approximately 12 hours apart (i.e., in the morning and in the evening) for one day. Concomitant use of ibrexafungerp with strong and moderate CYP3A inducers should be avoided.
Labeling	The Applicant's proposed labeling requires major edits. The review team has specific content and formatting change recommendations that will be communicated to the Applicant during labeling negotiations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 6-2 provides a summary of pharmacokinetic properties of ibrexafungerp.

Table 6-2. Pharmacokinetic Properties of Ibrexafungerp

Absorption	
Tmax (h)[a]	4-6
Distribution	
% bound to human plasma protein [b]	>99%
Volume of distribution (L) [c]	600
Elimination	
T1/2 (h) [d]	20
Major route(s) of elimination	Metabolism and biliary excretion
Metabolism	
Metabolic pathway(s)	Ibrexafungerp is subject to extensive hydroxylation followed by glucuronidation and sulfation of a hydroxylated metabolite. All metabolites observed in human liver and intestinal microsomes and human hepatocytes were considered minor (<10% parent) and pharmacologically inactive. The oxidative metabolism of ibrexafungerp (i.e., hydroxylation) in human liver microsomes is mainly mediated by CYP3A4 with CYP3A5 contributing to a lesser extent.
Excretion	
% dose excreted in feces [d]	88.4 (51 as unchanged ibrexafungerp)
% dose excreted in urine [d]	1.2

[a] Range of median values observed following 300 mg single dose (Study SCY-078-001) or 300 mg x 10 days (Study SCY-078-002) in healthy volunteers
[b] No evidence of concentration dependent protein binding; 99.6 to 99.8% binding observed in human plasma at concentrations of 0.1 to 10 µg/mL (SCY078-ADME-055)
[c] Mean value; no dose dependency was noted following IV administration in healthy subjects receiving multiple doses ranging from 30 mg to 375 mg twice daily for 3 days (SCY-078-106)
[d] Mean value following single dose administration of mg [14C]-ibrexafungerp salt form equivalent to 300 mg [14C] ibrexafungerp free drug in healthy subjects (SCY-078-116)

6.2.2. General Dosing and Therapeutic Individualization

The Applicant's proposed dosage regimen of ibrexafungerp is 300 mg (two 150 mg tablets) twice daily for one day for a total treatment dosage of 600 mg. This regimen is supported by the efficacy and safety results from the clinical trials submitted in the NDA.

Therapeutic Individualization

No clinically significant differences in the pharmacokinetics of ibrexafungerp were observed based on age, gender, or body weight. The effect of renal impairment on the pharmacokinetics

of ibrexafungerp has not been studied; however, the primary route of elimination of ibrexafungerp is by metabolism with renal excretion accounting for <2% of a dose.

The effect of hepatic impairment on the pharmacokinetics of ibrexafungerp was also not studied. The likelihood of accumulation or toxicity is low given the dose of ibrexafungerp in VVC is limited to a single day exposure (300 mg twice daily). Ibrexafungerp has been well tolerated at higher single day doses of 1600 mg in healthy subjects and 750 mg in patients with VVC.

Concomitant Use of CYP3A Inhibitors or CYP3A Inducers
Ibrexafungerp is a substrate of CYP3A4. Results from the drug-drug interaction study with ketoconazole (a strong CYP3A4 and P-gp inhibitor) showed that concomitant use of ketoconazole led to a 5.8-fold increase in ibrexafungerp AUC and 2.5-fold increase in Cmax. The Applicant proposed use with caution when ibrexafungerp is coadministered with strong CYP3A inhibitors. However, based on the acceptable safety profiles at single day doses up to 2.7-fold higher than the recommended single day dose of 600 mg of ibrexafungerp for the treatment of VVC and the short (single day) treatment duration, the Clinical Pharmacology review team recommends the following dosage regimen in patients with concomitant use of a strong CYP3A inhibitor: 150 mg twice daily for one day. No dosage adjustment is warranted in patients with concomitant use of a weak or moderate CYP3A inhibitor. See Section 6.3.2 for more information.

Although not studied in vitro or in vivo, CYP3A inducers are expected to significantly decrease the plasma concentration of ibrexafungerp. The Clinical Pharmacology review team recommends that concomitant use of strong and moderate CYP3A inducers be avoided. See Section 6.3.2 for more information.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Information on general pharmacology and pharmacokinetic characteristics is shown in Table 6-3.

Table 6-3. General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action	Ibrexafungerp, a triterpenoid antifungal agent, inhibits glucan synthase, an enzyme present in fungal, but not human cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall.
Active Moieties	Ibrexafungerp

QT Prolongation	At a concentration of 5 times or greater than that achieved after a single day 300 mg BID dose, ibrexafungerp does not prolong the QTc interval to any clinically relevant extent.
Bioanalysis	Multiple validated HPLC and LC-MS/MS assays were used to determine concentrations of ibrexafungerp in human plasma and urine. All bioanalytical assays met the requirements for specificity, sensitivity, accuracy, and precision.
Drug exposure at the therapeutic dosing regimen for VVC	Based on a population pharmacokinetic analysis, the model predicts that 300 mg twice a day for one day achieves a mean (%CV) AUC_{0-24} exposure of 6832 (15%) ng•hr/mL and C_{max} of 435 (15%) ng/mL under fasted conditions and a mean AUC_{0-24} exposure of 9867 (15%) ng.h/mL and C_{max} of 629 (15%) ng/mL under fed conditions for patients with VVC. In the population PK model, disease state (VVC) was determined to be a significant covariate. For a healthy subject (36 years old, median age of subjects included in the final population PK model), receiving the therapeutic dose of 300 mg twice daily for one day, Cmax and AUC0-24 were predicted to be 21% and 20% lower, respectively, compared to a VVC patient of the same age receiving the same treatment. However, this difference may be a result of the sparse sampling of VVC patients (Study SCY-078-204) and not a true effect of disease state on ibrexafungerp PK.
Range of effective dose or exposure	In the Phase 2 dose ranging study, doses of 450 mg twice a day, 300 mg twice a day on Days 1-3, and 300 mg twice a day on Day 1 showed similar clinical cure rates to fluconazole 150 mg x1. Both Phase 3 studies evaluated a single daily dose of 300 mg twice a day.
Maximally tolerated dose (MTD) or exposure	1600 mg oral ibrexafungerp, the highest tested dose in the SAD study, is considered to be the maximally tolerated single dose.
Dose Proportionality	The AUC and Cmax increase in a roughly dose-proportional manner at single doses of 10 mg to 1600 mg and multiple daily doses of 300 mg to 800 mg.
Variability	For the to be marketed ibrexafungerp citrate salt tablet formulation (150 mg), the inter-subject variability (%CV) in AUC0-inf and Cmax following single dose administration of 600 mg (4x150mg) to healthy subjects in the fasted state was 37% and 34%, respectively. In the same study, %CV in AUC0-inf and Cmax values in the fed state following a single 300 mg (2x150mg) dose was 20% and 28%, respectively, when normalized by dose. In simulated patients with VVC administered 300 mg ibrexafungerp twice daily for one day, the %CV in AUC0-24 and Cmax in the fasted state were 15% for both parameters. Similarly, %CV in AUC0-inf and Cmax values in the fed state were also 15% for both parameters. The reduced CV% in simulated VVC patients is reasonable given these simulations were generated using pooled clinical data from three studies (SCY-078-102, SCY-078-107 and SCY-078-204) and may be subject to correlation in covariates inherent to the dataset.

Food effect	Coadministration of ibrexafungerp citrate salt tablet (to be marketed formulation) with a high fat meal increases ibrexafungerp AUC by 38% and Cmax by 32%.
Substrate enzymes [in vitro]	Ibrexafungerp is a substrate of CYP3A4.
Substrate transporter systems [in vitro]	Ibrexafungerp is a substrate of P-glycoprotein.
Inhibition/Induction of Metabolism	Ibrexafungerp is a competitive inhibitor of CYP2C8 and CYP3A4 in vitro. Results from in vitro studies suggest ibrexafungerp does not induce CYP3A.
Inhibition/Induction of transporter systems	In vitro, P-gp, BCRP, BSEP, MRP2, and OATP1B3 transport activity were inhibited by ibrexafungerp in a concentration-dependent manner. OATP1B1, OCT1, OCT2, OAT1, and OAT3 activities were not inhibited by >50% in the presence of ibrexafungerp at the highest concentration studied (30 μM).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of effectiveness of ibrexafungerp for the treatment of postmenarchal females with VVC was provided by two Phase 3 studies, SCY-078-303 (VANISH 303) and SCY-078-306 (VANISH 306). Supportive evidence of effectiveness was provided by two Phase 2 studies, a proof of concept trial (SCY-078-203) and a dose finding trial (SCY-078-204) and animal studies demonstrating a 9-fold higher exposure in vaginal tissue than in blood (SCY078-ADME-035).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of ibrexafungerp, 300 mg (2 tablets of 150 mg) twice a day for one day for total treatment dosage of 600 mg, is appropriate for postmenarchal females with VVC.

This dose was studied in Phase 3 based on the results of Study SCY-078-204, a Phase 2 dose-finding trial in adult women with VVC. This Phase 2 study included treatment durations of 1 or 3 days and total doses ranging from 600 mg to 1800 mg, with a highest single daily dose of 750 mg. The primary efficacy endpoint was the percentage of subjects with Clinical Cure at the Test of Cure (TOC) visit. Clinical Cure rates for ibrexafungerp in the 300 mg twice a day for one day only group were 52% [14/27] in the mITT population, compared to 58% (14/24) for fluconazole. While the dosing regimens of 300 mg twice daily for 3 days and 450 mg twice daily for 1 day showed slightly higher clinical cure rates at TOC of 57.7% and 61.9%, respectively, the dosing regimen of 300 mg twice a day for one day showed the optimal balance of tolerability and efficacy when considering the totality of primary and secondary efficacy endpoints.

In both Phase 3 studies, the percentage of women with Clinical Cure at the TOC visit in the mITT population was statistically significantly higher for the ibrexafungerp group than the placebo

group (50.5% versus 28.6%; P=0.001 in VANISH 303 and 63.3% versus 44.0%; P=0.007 in VANISH 306). For more information see Section 8, Statistical and Clinical Evaluation.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinically significant differences in the pharmacokinetics of ibrexafungerp were observed based on age, gender, or body weight. Renal impairment is not expected to have an effect on the PK of ibrexafungerp since the primary route of elimination is metabolism. While the effect of hepatic impairment on the elimination of ibrexafungerp was not studied, the likelihood of toxicity or accumulation is low given the single day dosing regimen for VVC.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food Effect

Food intake increases the bioavailability of ibrexafungerp. Following administration of ibrexafungerp citrate salt tablet (to be marketed formulation) to healthy volunteers, Cmax increased 32% and AUC increased 38% with a high fat meal (800-1000 calories; 50% fat, compared to fasted conditions).

Table 6-4. Summary of Statistical Analyses for Ibrexafungerp Food Effect Comparison for the Citrate Salt Tablet

Ibrexafungerp Formulation	N	$AUC_{0\text{-}inf}$ (h*nM)	C_{max} (nM)	Tmax (h)
Citrate Salt Tablet- Dose Normalized ($AUC_{0\text{-}inf}$ and C_{max}/300 mg Dose), Crossover Subjects Only (Treatment A and E)				
300 mg -fed (E2)	9	11052 (7907, 15449)	420.6 (310.9, 586)	6 (6-8)
600 mg- fasted (A)	9	7997 (5721, 11179)	318 (228.2, 443)	4 (2-6)
GMR- E2/A Comparison		1.38 (0.95, 2.02)	1.32 (0.91, 1.92)	
p-value				0.0156

Source: Study SCY-078-107

The effect of food was also corroborated with a VVC population PK model which demonstrated that food (snack, standard meal, or high-fat meal) increased exposures (Cmax and AUC0-24) by approximately 44%.

The Applicant proposed that ibrexafungerp may be taken with or without food. The Applicant also suggests that the frequency of nausea is reduced when administered under fed conditions based on the results of study SCY-078-102 evaluating the food effect for investigational formulations. In this study, subjects who received ibrexafungerp citrate tablet (the 250 mg strength with identical quantitative composition as the 150 mg citrate salt tablet) in the fasted state experienced more nausea (4/24) as compared to subjects who received the study drug in the fed state (0/24). The clinical review team has concluded that these results provide

insufficient data to support the Applicant's claim as the number of subjects evaluated in this study is too small to draw conclusions about the effects of food on GI adverse reactions. Further, the rates of other relevant GI ADRs (e.g., diarrhea, abdominal pain and nausea) were similar when ibrexafungerp was administered in the fed or fasted state (Table 6-5).

Table 6-5. Study SCY-078-102: Most Common Adverse Events by Treatment Group

	Ibrexafungerp Dose Group	
MedDRA Preferred Term	**Citrate Tablets 500 mg (2 x 250 mg) Fasted (n=24)**	**Citrate Tablets 500 mg (2 x 250 mg) Fed (n=22)**
Diarrhea	6 (25%)	5 (22.7%)
Abdominal pain upper	1 (4.2%)	4 (18.2%)
Nausea	4 (16.7%)	0
Abdominal pain	2 (8.3%)	0
Dizziness	1 (4.2%)	1 (4.5%)
Headache	1 (4.2%)	1 (4.5%)

In the Phase 2 dose-finding study (SCY-078-204), ibrexafungerp was administered in the fasted state. While the two Phase 3 studies (SCY-078-303, SCY- 078-306) did not collect information regarding food intake in relation to study drug administration, it is likely that most subjects followed the recommendation of taking the study drug with food, as was stated in the informed consent form and in the dosing reminder section of the subject's diary.

The overall efficacy results from two Phase 3 studies (assumed fed) and the Phase 2 study (fasted) based on frequency of clinical cure (primary endpoint) and mycological eradication are consistent (Table 6-6). However, it is important to note the small sample size of SCY-078-204 in comparison to the two Phase 3 studies.

Table 6-6. Clinical Cure and Mycological Eradication at the TOC Visit: SCY-078-303, SCY- 078-306, SCY-078-204 – mITT

	SCY-078-303 (Assumed Fed)	SCY-078-306 (Assumed Fed)	SCY-078-204 (Fasted)
	Ibrexafungerp 300 mg BID (N=188)	Ibrexafungerp 300 mg BID (N=188)	Ibrexafungerp 300 mg BID (N=27)
Clinical Cure, n(%)	95 (50.5)	119 (63.3)	14 (51.9)
Mycological Eradication n(%)	93 (49.5)	110 (58.5)	17 (63)

The overall safety conclusions from two Phase 3 studies (assumed fed) and the Phase 2 study (fasted) also are consistent, as illustrated by Table 6-7 which compares the frequency of the most common TEAEs reported in these studies.

Table 6-7. TEAEs at 5% Frequency or Greater in SCY-078-303 and SCY-078-306 Compared to Study SCY-078-204 - Safety Population

	SCY-078-303 and SCY-078-306 (Assumed Fed)	SCY-078-204 (Fasted)
Preferred Term	Ibrexafungerp 300 mg BID (N=545) n (%)	Ibrexafungerp 300 mg BID (N=30) n (%)
Diarrhea	91 (16.7%)	5 (16.7)
Nausea	65 (11.9%)	3 (10%)
Abdominal Pain[1]	45 (8.3%)	1 (3.3%)

[1] Combined Abdominal Pain, Abdominal Pain Upper and Abdominal Pain Lower

The Clinical Pharmacology review team agrees that ibrexafungerp may be taken with or without food based on the conclusion that the effect of food on exposure of ibrexafungerp is not expected to noticeably impact the safety or efficacy of the single day oral ibrexafungerp dose regimen proposed for VVC.

Drug-Drug Interactions (DDIs)

Effect of CYP3A Inhibitors on Ibrexafungerp Pharmacokinetics

In vitro studies showed ibrexafungerp is a substrate of CYP3A4 and P-gp. Clinical DDI studies were conducted to evaluate the effect of ketoconazole (strong inhibitor of CYP3A and P-gp) and diltiazem (moderate inhibitor of CYP3A4) on the pharmacokinetics of ibrexafungerp.

Ketoconazole increased ibrexafungerp AUC∞ by 5.8-fold and Cmax by 2.5-fold after subjects were administered ketoconazole 400 mg for 15 days starting at Day -1 with a single dose of 50 mg ibrexafungerp co-administered on Day 1 (Study SCY-078-008; Table 6-8). While the contribution of intestinal P-gp inhibition cannot be definitively quantified, CYP3A4 inhibition is likely the main driver of this interaction given metabolism is the primary route of elimination. The increase in AUC and Cmax demonstrated with concomitant use of diltiazem (a moderate CYP3A4 inhibitor) further reinforces the significant role of CYP3A4 inhibition (see below).

Table 6-8. Summary of Statistical Analysis for Ibrexafungerp by Treatment Per-Protocol Population

Treatment	N	LS Geometric Mean (95% CI)			T_{max} (hr) [c]	$T_{1/2}$ (hr) [d]
		$AUC_{0\text{-}inf}$ (nM*hr)	$AUC_{0\text{-}24}$ (nM*hr)	C_{max} (nM)		
Ibrexafungerp Alone [a]	12	795.12 (628, 1006.72)	459.65 (380.05, 555.94)	36.13 (30.03, 43.47)	2 (1-6)	20.3 ± 3.3
Ibrexafungerp + Ketoconazole [b]	10	4579.06 (3536.06, 5929.69)	1474.9 (1197.53, 1816.53)	91.15 (74.44, 111.62)	6 (4-8)	38.4 ± 12.2
GMR [e]		5.76 (4.31, 7.69)	3.21 (2.54, 4.05)	2.52 (2.01, 3.17)		

Source: Study SCY-078-008

[a] AUC following single dose administration of 50 mg ibrexafungerp (Period 1)

[b] AUC following 400 mg ketoconazole for 15 days starting at Day -1 with a single dose of 50-mg ibrexafungerp coadministered on Day 1 (Period 2, administered to all subjects from Period 1 A following a washout period of at least 7 days)

[c] Median (Min-Max)

[d] Harmonic Mean ± Pseudo SD

[e] Geometric Mean Ratio, ibrexafungerp + ketoconazole/ibrexafungerp alone (90% CI)

Diltiazem increased ibrexafungerp AUC by 2.5-fold and Cmax by 2.2-fold after subjects were administered diltiazem 240 mg once daily for 15 days starting on Day -1 with a multiple dose

ibrexafungerp regimen of 200 mg three times daily (total dose of 600 mg) on Day 1 followed by 100 mg ibrexafungerp once daily Days 2 to 14 (Study SCY-078-016; Table 6-9).

Table 6-9. Summary of Statistical Analysis for Ibrexafungerp by Treatment – Per-Protocol Population

Treatment	N	LS Geometric Mean (95% CI)			T_{max} (hr) [b]	$T_{1/2}$ (hr) [c]
		$AUC_{0\text{-}24hr}$ (nM*hr)	C_{max} (nM)	C_{24} (nM)		
Ibrexafungerp Alone	16	2452 (2135, 2816) [a]	164.5 (146.6, 184.5)	58.58 (49.68, 69.07)	5 (3-6)	14 ± 3.2
Ibrexafungerp + Diltiazem	15	6179 (5355, 7129) [b]	363.2 (322.6, 408.9)	182.2 (153.7, 216)	5 (4-6)	20.7 ± 3.6
GMR [d]	15	2.52 (2.14, 2.97)	2.21 (1.93, 2.53)	3.11 (2.55, 3.79)		

Source SCY-078-016
[a] $AUC_{0\text{-}24hr}$ value at Day 14 following ibrexafungerp three times daily (total dose of 600 mg) on Day 1, and 100 mg of ibrexafungerp daily on Days 2 to 14 (Treatment A).
[b] $AUC_{0\text{-}24hr}$ value at Day 14 following 240 mg of diltiazem daily on Days -1 to 14 and 200 mg of ibrexafungerp three times daily (total dose of 600 mg) on Day 1 followed by 100 mg of ibrexafungerp daily on Days 2 to 14 (Treatment B, administered to all subjects from treatment group A following a washout period of at least 14 days).
[b] Median (Min-Max)
[c] Harmonic Mean ± Pseudo SD
[d] Geometric Mean Ratio, ibrexafungerp + diltiazem/ibrexafungerp alone (90% CI) on Day 14

The Applicant proposed use with caution when ibrexafungerp is co-administered with strong CYP3A4 inhibitors. In addition, the Applicant proposed labeling states co-administration of ibrexafungerp with strong CYP3A4 inhibitors may require dose adjustment, although no specific dose adjustment was proposed.

Results from Phase 1 studies showed that ibrexafungerp was well tolerated following oral administration at single day doses up to 1600 mg and multiple daily doses up to 800 mg per day for 28 days. Given 1) dose proportional increase in ibrexafungerp AUC following single dose administration from 10 to 1600 mg, 2) the acceptable safety profiles of ibrexafungerp at single day doses up to 1600 mg [2.7-fold higher than the recommended daily dose of 600 mg], and 3) short (single day) treatment duration of ibrexafungerp for the treatment of VVC, the Clinical Pharmacology review team recommends the following dose reduction in patients concomitantly using a strong CYP3A inhibitor: 150 mg twice daily for one day. Dose adjustment is not warranted when ibrexafungerp is concomitantly administered with mild or moderate CYP3A inhibitors.

Effect of CYP3A Inducers on Ibrexafungerp Pharmacokinetics
The Applicant did not investigate the effect of CYP3A inducers on ibrexafungerp Pharmacokinetics. However, CYP3A inducers are expected to have a significant effect on ibrexafungerp exposure given ibrexafungerp is a CYP3A4 substrate and coadministration of ketoconazole (a strong CYP3A4 inhibitor) increased the ibrexafungerp $AUC_{0\text{-}inf}$ by 5.8-fold and C_{max} by 2.5-fold. The lowest dose evaluated in the Applicant's Phase 2 dose ranging study was 150 mg twice a day for 3 days (e.g., a two-fold decrease in single day exposure). The clinical cure rate at TOC with 150 mg twice daily for 3 days was similar to that observed following the clinical dose of 300 mg twice daily for 1 day (48% vs. 52%, respectively); however, the impact of

duration of therapy on efficacy was not evaluated. Given the unknown implications of CYP3A inducers on ibrexafungerp pharmacokinetics, the Clinical Pharmacology review team recommends that concomitant use of strong and moderate CYP3A inducers be avoided.

Effect of Proton Pump Inhibitors on Ibrexafungerp Pharmacokinetics
Results from solubility studies in pH buffers indicate the solubility behavior of ibrexafungerp citrate is pH dependent with the highest solubility in acidic pH and progressively decreasing with increasing pH. Given proton pump inhibitors (PPIs) effectively block gastric acid secretion and increase gastric pH, the Applicant conducted a clinical DDI study to evaluate ibrexafungerp exposure when coadministered with a PPI, pantroprazole (Study SCY-078-015). Results from this study showed that pantoprazole decreased ibrexafungerp AUC0-inf by 25% following multiple dose administration of 40 mg pantoprazole delayed release tablet once daily on Days -4 to Day 1 coadministered with a single dose of 500 mg ibrexafungerp on Day 1 under fasted conditions (approximately 2.5 hours after pantoprazole dosing) compared to ibrexafungerp alone (Study SCY-078-015; Table 6-10).

Table 6-10. Summary of Pharmacokinetic Parameters of Ibrexafungerp Tablet and Ibrexafungerp Tablet Co-administered with Pantoprazole

PK Parameter	Ibrexafungerp Tablet (B)			Ibrexafungerp Tablet + PPI (C)			Ratio (C/B)	
	N	GM	95 % CI	N	GM	95% CI	GMR	90% CI
AUC0-inf (hr*ng/mL)	15	7804.01	(6232.88, 9771.17)	14	5904.40	(4885.05, 7772.93)	0.757	(0.615, 0.930)
Cmax (ng/mL)	15	372.45	(301.74, 459.73)	14	290.15	(210.71, 399.53)	0.779	(0.612, 0.991)
Tmax (hr)	15	4.02	3.97-6.0	14	4.06	2.0-8.0	-	-
T1/2	15	21.79	17.05%	14	22.64	22.52%		

Source: Study SCY-078-015
CI = confidence interval; GM = geometric mean

This study used a lower limit 90% CI for AUC0-inf GMR (with PPI / without PPI) of >0.60 to satisfy the hypothesis that the pharmacokinetics of ibrexafungerp were similar with or without a PPI based on the variability of ibrexafungerp exposure after oral administration. To derive this lower limit, the Applicant used a CV of 38.37% for AUC0-inf from healthy volunteers who received 300 mg of the to-be-marketed citrate salt tablet twice daily for 1 day following a standard low-fat meal (Study SCY-078-107). The dose normalized AUC0-inf in the fasted state from this study was associated with a CV of 37%. Based on the non-effect boundaries defined in this study, the DDI interaction with pantoprazole was not considered to be significant.

The ibrexafungerp exposure following concomitant PPI administration is expected to fall within the range of efficacious exposures in the clinical studies. An analysis of outcome was done in women receiving PPIs in these two Phase 3 studies. Only 22 subjects enrolled in these studies reported taking PPIs, 10 of which received ibrexafungerp. Four of these 10 subjects had Clinical Cure at TOC and five of them had Mycological Eradication at TOC. However, it is not possible to

draw definitive conclusions from this information given the small sample size and limited number of women receiving PPIs in these studies. An exposure-response relationship was not available for evaluation given PK samples were not collected in either Phase 3 study.

In the Applicant's Phase 2 dose ranging study, 150 mg twice a day for 3 days showed a similar clinical cure rate at TOC to the clinical dose of 300 mg twice daily for one day (48% vs. 52%, respectively). While the impact of duration of therapy on efficacy was not evaluated, these results also suggest that ibrexafungerp exposure following concomitant PPI administration falls within the range of efficacious exposures. The Clinical Pharmacology review team agreed that a 25% decrease in ibrexafungerp exposure when coadministered with a PPI is unlikely to significantly impact ibrexafungerp efficacy in VVC patients.

Effect of Ibrexafungerp on the Pharmacokinetics of Other Drugs
In vitro, ibrexafungerp was shown to be an inhibitor of CYP2C8, CYP3A4, P-gp, and OATP1B3. Clinical DDI studies evaluating the inhibition potential of ibrexafungerp towards these CYP enzymes and transporters were conducted at doses and exposures higher than the recommended dose of ibrexafungerp for VVC (Table 6-11). Given 1) the single day treatment duration for VVC of 300 mg twice a day and 2) the higher doses of 750 mg once daily for 3-7 days with or without a 1250 mg loading dose evaluated in these studies, the effect of ibrexafungerp on the pharmacokinetics of substrates of CYP2C8, CYP3A4, P-gp, and OATP1B3 transporters is considered to be not clinically significant (See Section 16.3 for more information).

Table 6-11. Effect of Ibrexafungerp on Pharmacokinetics of Coadministered Drugs

	Type of Substrate	Ibrexafungerp Dose	Effect on Coadministered Medication Exposure
Tacrolimus	CYP3A4 and P-gp	1250 mg on Day 1 followed by 750 mg once daily for 7 days	1.4-fold increase in $AUC_{0\text{-}inf}$ and no effect on C_{max}
Dabigatran	P-gp	750 mg twice daily on Days 1 and 2 followed by 750 mg daily on Days 3 and 4	1.4-fold increase in $AUC_{0\text{-}48}$ and 1.25-fold increase in C_{max}
Pravastatin	OATP1B1 and OATP1B3	750 mg twice daily on Days 1 and 2 followed by 750 mg daily on Day 3	2.8-fold increase in $AUC_{0\text{-}24}$ and 3.5-fold increase in C_{max}
Rosiglitazone [a]	CYP2C8	1250 mg ibrexafungerp on Day 1 followed by 750 mg once daily for 7 days	No change in $AUC_{0\text{-}inf}$ or C_{max}

Source: Studies SCY-078-103, SCY-078-108, SCY-078-115
[a] Rosiglitazone is a moderate sensitive substrate of CYP2C8

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7-1. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled[1]	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
SCY-078-303 (VANISH 303)	NCT03734991	Multicenter, Double- Blind, Randomized, Placebo-Controlled	Ibrexafungerp (citrate) 150 mg oral tablets Randomized 2:1 -Ibrexafungerp 300mg PO BID (600 mg TDD) x 1d -Matching placebo PO BID x 1d	1° Clinical cure at TOC visit (Day 11±3) 2° Mycological eradication at TOC, Clinical cure and mycological eradication at TOC, Complete resolution at FU visit (Day 25±4), Clinical improvement at TOC, Absolute clinical score change at TOC and FU, Safety and tolerability	Duration 1 day Follow-up 25±4 days	371 total (247 active, 124 placebo)	Acute VVC Post-menarchal females ≥12 y	27 U.S. sites FPFV 04 Jan 2019 LPLV 04 Sep 2019
SCY-078-306 (VANISH 306)	NCT03987620 EudraCT 2018-00449	Multicenter, Double- Blind, Randomized, Placebo-Controlled	Ibrexafungerp (citrate) 150 mg oral tablets Randomized 2:1 -Ibrexafungerp 300mg PO BID (600 mg TDD) x 1d -Matching placebo PO BID x 1d	1° Clinical cure at TOC visit (Day 11±3) 2° Mycological eradication at TOC, Clinical cure and mycological eradication at	Duration 1 day Follow-up 25±4 days	449 total (298 active, 151 placebo)	Acute VVC Post-menarchal females ≥12 y	37 sites (19 U.S., 18 Bulgaria) FPFV 07 Jun 2019 LPLV 07 Feb 2020

	2-12			TOC, Complete resolution at FU visit (Day 25±4), Clinical improvement at TOC, Absolute clinical score change at TOC and FU, Safety and tolerability				
		Studies to Support Safety						
SCY-078-106		Single-center, Randomized, Placebo-Controlled, Safety and PK study *(submitted in lieu of dedicated TQT study)*	Ibrexafungerp SBECD IV formulation Part 1: SAD IV 30 mg, 60 mg, 125 mg, 250 mg, 375 mg (as 1.5 mg/mL or 0.75 mg/mL solution) Part 2: MAD IV *Planned:* loading dose then daily or BID dosing x 10d *Actual:* 60 mg loading dose then 30 mg daily or BID for 3-6 doses total	1° safety, tolerability, PK 2° cardiodynamic assessments, urinary excretion	Duration *Planned:* up to 10 d *Actual:* up to 4d Dosing terminated after Day 4 in MAD phase due to local tolerability issues	Planned: 48 Enrolled: 32 Completed: 20	Healthy adults 18-50y	1 U.S. site
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)[2]						
SCY-078-203	NCT02679456	Multi-center, Randomized, Evaluator Blinded, Active-Controlled Proof of Concept Study	Ibrexafungerp (phosphate) 250 mg tablets Randomized 1:1:1 Group 1: Fluconazole 150 mg PO x 1 Group 2: Ibrexafungerp 1250	1° Therapeutic cure (clinical cure and mycological eradication) at TOC (Day 24±3) 2° Therapeutic	Duration 3-5 d Follow-up 120±3 days	96 total (64 active, 32 fluconazole)	Moderate-to severe VVC with ≥3 episodes/y 18-65y	2 sites in Dominican Republic FPFV 17 Nov 2015

			mg PO x 1 on Day 1 then 750 mg PO daily through Day 3 Group 3: Ibrexafungerp 1250 mg PO x1 on Day 1 then 750 mg daily through Day 5	cure at 2 mo, 3 mo, 4 mo; Clinical cure at TOC, 2 mo, 3 mo, 4 mo; Mycological eradication at TOC, 2 mo, 3 mo, 4 mo; Recurrence at TOC, 2 mo, 3 mo, 4 mo; Clinical score at TOC, 2 mo, 3 mo, 4 mo;		32 3-day active, 32 5-day active		LPLV 05 Aug 2016
SCY-078-204 (DOVE)	NCT03253094	Multicenter, Double-Blind, Randomized, Double-Dummy, Active-Controlled, Dose-Finding Study	Ibrexafungerp (citrate) 150 mg oral tablets Group 1: Ibrexafungerp 750mg PO daily x 1d Group 2: Ibrexafungerp 300mg PO BID x 1d Group 3: Ibrexafungerp 450mg PO BID x 1d Group 4: Ibrexafungerp 150mg PO BID x 3d Group 5: Ibrexafungerp 300mg PO BID x 3d Group 6: Fluconazole 150mg PO daily x 1d	1° Clinical cure at TOC visit (Day 10±2) 2° Mycological eradication at TOC, Clinical cure and mycological eradication at TOC and at FU visit (Day 25), Continued clinical response at FU, Time to resolution of signs and symptoms	Duration 1-2 d Follow-up 25±4 days	185 total (153 active, 32 fluconazole) 32 in each dosing group	Moderate-to severe VVC ≥18y	25 U.S. sites FPFV 02 Aug 2017 LPLV 01 May 2018

TDD, total daily dose; BID, twice daily; TOC, test of cure; FU, follow-up; VVC, vulvovaginal candidiasis; FPFV, first patient first visit; LPLV, last patient last visit; PK, pharmacokinetic; SAD, single ascending dose; MAD, multiple ascending dose
[1]Reported number of subjects enrolled and receiving at least one dose of study treatment
[2]Phase 1 studies included in the oral ibrexafungerp safety population are summarized in Table 24
Source: Clinical reviewer

7.2. Review Strategy

The sources of data used in the evaluation of efficacy and safety of oral ibrexafungerp included data sets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] which can be found at the following links: \\cdsesub1\evsprod\NDA214900\0001 and \\cdsesub1\evsprod\NDA214900\0008.

Patient-level data from the VANISH-303 (SCY-078-303) and VANISH-306 (SCY-078-306) trials were used to evaluate the efficacy of oral ibrexafungerp compared to placebo for the treatment of females with VVC.

The primary source of safety data was the treatment-emergent adverse events and laboratory data reported from the pooled safety populations in the VANISH-303 and VANISH-306 trials. Potential adverse drug reactions were identified by evaluation of events occurring at increased frequency in subjects receiving oral ibrexafungerp compared to those receiving placebo. Additional supportive safety data were provided by the adverse event reports and laboratory monitoring from two Phase 2 studies of oral ibrexafungerp enrolling women with VVC and 15 Phase 1 studies of oral ibrexafungerp in healthy adult volunteers.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study SCY-078-303

Trial Design

Study 303 was a randomized, double-blind, placebo-controlled, multicenter study designed to assess the efficacy and safety of ibrexafungerp compared to placebo in the treatment of female subjects 12 years and older with acute VVC. The design of the study followed the Guidance for Industry: Developing drugs for the treatment of VVC (draft version July 2016 subsequently finalized in August 2019 during the conduct of the study). The study was conducted at 27 sites in the United States. The study was started on January 4, 2019 and completed on September 4, 2019.

Eligible subjects included postmenarchal females aged ≥12 years with a diagnosis of symptomatic acute VVC. A diagnosis of symptomatic acute VVC required 1) a minimum composite vulvovaginal signs and symptoms (VSS) score of ≥ 4 with at least 2 signs or symptoms having a score of 2 or greater at baseline; 2) positive microscopy with 10% KOH in a vaginal sample collected at screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts; and 3) normal vaginal pH (≤4.5). Vulvovaginal signs (edema, erythema, and excoriation) and symptoms (burning, itching, and irritation) were assessed by the investigator and subject, respectively. Each sign and symptom was scored based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) and the individual scores summed to calculate the total composite VSS score. Subjects were not eligible if they had any vaginal condition other than acute VVC that may have interfered with the diagnosis or evaluation of response to therapy, such as suspected or confirmed concurrent causes of vulvovaginitis and/or cervicitis including bacterial vaginosis, *Trichomonas vaginalis*, *Herpes* virus, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, symptomatic human papillomavirus, or other mixed infections; received systemic and/or topical (vaginal) antifungal treatment, including prescription or over-the-counter products, within 28 days of the baseline visit; had active menstruation at the baseline visit; had uncontrolled diabetes mellitus; or had a history of or an active cervical/vaginal cancer.

Eligible subjects were randomized in a 2:1 ratio to receive oral ibrexafungerp (300 mg dose twice daily) or matching placebo administered twice daily for 1 day. Randomization was stratified by the presence or absence of a diagnosis of diabetes mellitus.

Study visits were conducted at screening/baseline on Day 1, a test of cure (TOC) visit on Day 11 (± 3 days), and a follow-up (FU) visit on Day 25 (± 4 days). On Day 1, subjects were dispensed study medication and a subject diary. The subject diary was used to rate vulvovaginal symptoms of infection and record study drug dosing details, AEs, and concomitant medication use daily from Day 1 through the TOC visit. Vulvovaginal symptoms were reported by the

subject at all clinic visits. Vulvovaginal signs were assessed by the investigator at screening and the TOC visits, and at the FU visit if symptoms were reported by the subject. Vaginal samples for fungal culture were taken at screening and the TOC visits, and at the FU visit if symptoms were reported by the subject.

***Reviewer's Comment**: Since ibrexafungerp is a single day treatment, a TOC visit at Day 8-14 is as recommended in the guidance for the treatment of VVC.*

A Phase 2b dose-finding study was conducted to determine the dose to be studied in Phase 3. The selected dose of ibrexafungerp (300 mg BID for 1 day) was the dose that was determined by the Applicant to have shown meaningful clinical and microbiological response rates with adequate tolerability. Placebo controls are the preferred controls for treatment of acute VVC studies.

Study Endpoints

The primary efficacy endpoint is clinical cure at the TOC visit. Clinical cure is defined as complete resolution of signs and symptoms (VSS score =0) without need for further antifungal treatment prior to or at the visit. Subjects who terminated before the TOC visit and received additional antifungal treatment prior to or at the early termination visit were considered a clinical failure.

Secondary endpoints include mycological eradication (negative culture for growth of *Candida* species) at the TOC visit, overall success (clinical cure and mycological eradication) at the TOC visit, complete resolution of symptoms at the FU visit, and clinical improvement at the TOC visit. Clinical improvement is defined as a total VSS score ≤1. Subjects who received additional antifungal treatment were considered a clinical failure/mycological persistence at any visit at and after the receipt of additional anti-fungal treatment.

***Reviewer's Comments**: Complete resolution of all vulvovaginal signs and symptoms is the primary endpoint as recommended in the guidance for the treatment of VVC. Although not included in the guidance, the Applicant also assessed clinical improvement which allowed a subject to have a single mild sign or symptom to be present as they felt this was also indicative of an acceptable response for the subject.*

Since the TOC visit was the early visit, a vulvovaginal exam was not required per the protocol at the FU visit unless the subject was experiencing symptoms. Therefore, the vaginal signs are not considered missing in this situation. When a subject did not have vaginal signs assessed at the FU visit because they did not present with symptoms, the total VSS score was calculated as 0.

Statistical Analysis Plan

The statistical analysis plan (SAP) was finalized on October 16, 2019, prior to database lock.

<u>Analysis Populations</u>

The ITT population includes all randomized subjects who signed the informed consent form and received at least one dose of study drug.

The modified ITT (mITT) population includes all randomized subjects who had a positive culture for *Candida* species at baseline and received at least one dose of study drug.

The per-protocol (PP) population includes all mITT subjects who completed study drug treatment, had a TOC (or early termination TOC; a change to that stated in the SAP) evaluation that included documentation of signs, symptoms, and collection of a vaginal culture, and had no major protocol deviation.

The primary analysis population for efficacy is the mITT population. The ITT and PP populations were considered supportive.

The safety set includes all subjects randomly assigned to receive study drug who received at least one dose of study drug and had at least one postbaseline evaluation.

Reviewer's Comment: *For the efficacy analyses, the focus of this review is the mITT population. It should be noted that the clinical study report for the identically designed Study 306 indicated a change in the definition of the mITT population used in the clinical study report from that stated in the Study 306 SAP (see discussion under Study 306). Although not stated in the clinical study report for Study 303, upon review of the Data Definition file for Study 303, it was noted that the same definition was applied for Study 303. The Division does not agree to the change in definition for the mITT population. Therefore, the Applicant was asked (Request for Information dated November 19, 2020) to revise the mITT population to be based on the definition stated in the SAP, update the ADSL dataset to include a flag for this population, and rerun the primary efficacy analyses based on this population. The Applicant provided a response to this information request on December 11, 2020. In this review, all discussions and tables presented regarding the mITT population are based on the SAP-stated definition.*

To be aligned with the SAP written for the identically designed Study 306, the PP protocol definition in Study 303 was revised in the clinical study report to allow for the inclusion of subjects who had an early termination TOC visit instead of a TOC visit. There are no concerns with this change as it ensures that the early treatment failures are included in the analysis.

Analysis Methods

The primary analysis was a comparison of the proportion of subjects with clinical cure at the TOC visit in the ibrexafungerp group versus the placebo group. A Cochran-Mantel-Haenszel (CMH) test adjusted for site and diabetes mellitus diagnosis was conducted to assess the statistical significance of the difference between treatment groups. The p-value, relative risk and 95% confidence interval were calculated. Additionally, the difference in proportions (ibrexafungerp – placebo) and corresponding 95% confidence interval based on the Miettinen and Nurminen method were calculated.

The secondary endpoints were analyzed using same methods as the primary endpoint. For the categorical endpoints (primary and secondary), missing responses were imputed as non-responders (failures, mycological persistence) in the analyses.

Reviewer's Comment: *It should be noted that the SAP for Study 303 stated that the odds ratio rather than relative risk would be calculated. The clinical study report for Study 303 reports the relative risk. This is in alignment with the SAP written for the identically designed Study 306. This change is acceptable. It does not impact the integrity of the trial and the results are consistent across the various methods.*

Sample Size Calculation

Assuming clinical cure rates at TOC of 50% for ibrexafungerp and 30% for placebo and a 2:1 randomization, approximately 282 subjects were expected to provide 90% power to detect a difference between the treatment groups with a type 1 error rate of 5%. It was further assumed that approximately 20% of subjects would not have a mycological culture-confirmed infection at baseline and approximately 10% of subjects may withdraw early from the study. Therefore, the sample size was increased by 84 subjects for a total of 366 subjects (244 subjects randomized to ibrexafungerp and 122 subjects randomized to placebo).

Interim Analysis

No interim analysis of efficacy data was conducted.

Protocol Amendments

There were no amendments to the original protocol dated October 12, 2018.

Study Results

Compliance with Good Clinical Practices

The Applicant states that "The study was conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Council for Harmonisation (ICH) tripartite guideline E6: Good Clinical Practice (GCP) guidelines, the US Code of Federal Regulations sections that address clinical research studies, applicable European Union regulations, and/or other national and local ethical and legal requirements, as applicable."

Financial Disclosure

The Applicant certified that they had not entered into any financial arrangements with the clinical investigators in Study 303 whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), the investigators did not

have any proprietary interest in the product or significant interest in the trial sponsor, and the clinical investigators were not recipients of significant payments of other sorts.

Patient Disposition

A total of 376 subjects were randomized in the study. Five subjects (2 ibrexafungerp and 3 placebo) did not receive any study medication and were excluded from all efficacy and safety analyses. All treated subjects received the treatment to which they were randomized. Therefore, the ITT and the Safety populations are the same and include 247 ibrexafungerp subjects and 124 placebo subjects. A total of 57 (23.1%) ibrexafungerp subjects and 24 (19.4%) placebo subjects did not have yeast isolated at baseline and were excluded from the mITT population. The per-protocol population excluded an additional 12 ibrexafungerp subjects and 6 placebo subjects for protocol deviations. The analysis populations are summarized in Table 8-1.

Table 8-1: Analysis Populations for Study 303

Analysis Population	Ibrexafungerp N (%)	Placebo N (%)	Total N (%)
Randomized	249 (100)	127 (100)	376 (100)
ITT/Safety*	247 (99.2)	124 (97.6)	371 (98.7)
mITT**	190 (76.9)	100 (80.6)	290 (78.2)
Per-protocol**	178 (72.1)	94 (75.8)	272 (73.3)

Source: Reviewer conducted analysis using ADSL dataset
*% of randomized subjects
**% of ITT population

In the ITT population, 5 ibrexafungerp subjects did not complete treatment. Two of these subjects did not take the second dose due to an adverse event. The other 3 subjects withdrew from the study and did not return their diaries; therefore, receipt of the second dose could not be verified. All placebo subjects in the ITT population completed both doses of study treatment.

A total of 183 (74.1%) ibrexafungerp subjects and 80 (64.5%) placebo subjects in the ITT population completed the study. The primary reason for premature discontinuation from the study was lack of efficacy and/or use of antifungal therapy prior to or at the TOC visit. A higher percentage of placebo subjects (31.5%) compared to ibrexafungerp subjects (19.4%) discontinued for this reason. Four ibrexafungerp subjects (1.6%) compared to no placebo subjects discontinued the study due to an adverse event. Subject disposition including the reason for discontinuing treatment and the study is summarized in Table 8-2.

Table 8-2: Subject Disposition in Study 303 (ITT Population)

	Ibrexafungerp (N=247) n (%)	Placebo (N=124) n (%)

Completed Treatment	242 (98.0)	124 (100)
Discontinued Treatment	5 (2.0)	0
Adverse event	2 (0.8)	0
Lost to follow-up/Patient withdrawal	3 (1.2)	0
Completed Study	183 (74.1)	80 (64.5)
Discontinued Study	64 (25.9)	44 (35.5)
Lack of efficacy and/or use of antifungal therapy prior to TOC	48 (19.4)	39 (31.5)
Use of antifungal therapy after TOC	1 (0.4)	2 (1.6)
Adverse event	4 (1.6)	0
Lost to follow-up	4 (1.6)	0
Physician Decision	0	1 (0.8)
Pregnancy	1 (0.4)	0
Withdrawal by Subject	4 (1.6)	0
Other	2 (0.8)	2 (1.6)

Source: Tables 5-1 and 5-11 of Study 303 Clinical Study Report and confirmed by Reviewer using ADSL dataset

Protocol Violations/Deviations

Major protocol deviations in the ITT population are summarized in Table 8-3. At least 1 major protocol deviation was reported for 11 (4.5%) ibrexafungerp subjects and 6 (4.8%) placebo subjects. One placebo subject had 2 major protocol deviations. For ibrexafungerp subjects, the most commonly reported major protocol deviations were due to study treatment compliance followed by not meeting inclusion/exclusion criteria. For placebo subjects, the most commonly reported major protocol deviation was not meeting inclusion/exclusion criteria. The reported protocol deviations are not expected to have had an impact on safety or efficacy analyses and the overall study results.

Table 8-3: Major Protocol Deviations in Study 303 (ITT Population)

Category	**Ibrexafungerp** (N=247) n (%)	**Placebo** (N=124) n (%)
At least 1 major protocol deviation	11 (4.5)	6 (4.8)
Inclusion/Exclusion Criteria	4 (1.6)	4 (3.2)
Study procedures/assessments	1 (0.4)	2 (1.6)
Study treatment compliance	5 (2.0)	0
Other protocol deviation	1 (0.4)	1 (0.8)

Source: Adapted from Table 5-3 of Study 303 Clinical Study Report
Note: 1 placebo subject had more than one major protocol deviation

Demographic and Other Baseline Characteristics

Table 8-4 summarizes demographic and baseline characteristics of subjects in the mITT population. There were no significant differences between the treatment groups. Approximately 55% of the subjects were White and 40% were Black. The median age was 33 years and the majority were in the 18 to less than 36 years age group. Although enrollment was open to adolescents, only a single subject less than 18 years was enrolled, and this subject

received placebo. The median body mass index was 28.3 and approximately one-third of the subject were classified as normal weight. Less than 10% of subjects were diabetic.

C. albicans was the most commonly identified species at baseline (n=175 or 92.1% for ibrexafungerp and n= 92 or 92% for placebo) followed by *C. glabrata* (n= 11 or 5.8% for ibrexafungerp and n=1 or 11% for placebo). Five ibrexafungerp subjects and 6 placebo subjects had mixed *Candida* infections. The median composite VSS score at baseline was 9 and ranged from 4 to 18. Few subjects reported having a history of VVC (3.2% for ibrexafungerp and 3.0% for placebo).

Table 8-4: Demographic Characteristics in Study 303 (mITT population)

Parameter	**Ibrexafungerp** (N=190) n (%)	**Placebo** (N=100) n (%)	**Total** (N=290) n (%)
Sex			
Female	190 (100)	100 (100)	290 (100)
Race			
White	103 (54.2)	55 (55.0)	158 (54.5)
Black	74 (39.0)	43 (43.0)	117 (40.3)
Asian	4 (2.1)	0	4 (1.4)
Other	9 (4.8)	2 (2.0)	11 (3.8)
Ethnicity			
Hispanic	55 (29.0)	19 (19.0)	74 (25.5)
Not Hispanic	135 (71.0)	81 (81.0)	216 (74.5)
Age (years)			
Mean (sd)	33.4 (10.4)	35.9 (12.4)	34.2 (11.2)
Median	32	34	33
Min, Max	18, 67	17, 66	17, 67
<18	0	1 (1.0)	1 (0.3)
18 to 35	108 (56.8)	56 (56.0)	164 (56.6)
36 to 49	71 (37.4)	27 (27.0)	98 (33.8)
50 to 64	10 (5.3)	14 (14.0)	24 (8.3)
≥ 65	1 (0.5)	2 (2.0)	3 (1.0)
Body Mass Index (kg/m^2)			
Mean (sd)	29.8 (8.5)	30.1 (8.0)	29.9 (8.3)
Median	28.2	29.1	28.3
Min, Max	17.9, 62.0	17.2, 53.7	17.2, 62.0
Underweight (<18.5)	3 (1.6)	1 (1.0)	4 (1.4)
Normal (18.5-<25)	67 (35.3)	33 (33.0)	100 (34.5)
Overweight (25-<30)	40 (21.1)	20 (20.0)	60 (20.7)
Obese (30-<40)	58 (30.5)	34 (34.0)	92 (31.7)
Morbidly obese (≥40)	22 (11.6)	12 (12.0)	34 (11.7)
Diabetes Mellitus			
Yes	18 (9.5)	8 (8.0)	26(9.0)
No	172 (90.5)	92 (92.0)	364 (91.0)
***Candida* species at baseline**			
C. albicans	170 (89.5)	87 (87.0)	257 (88.6)

C. albicans + C. glabrata	4 (2.1)	4 (4.0)	8 (2.8)
C. albicans +C. lusitaniae	1 (0.5)	1 (1.0)	2 (0.7)
C. dubliniensis	2 (1.0)	0	2 (0.7)
C. glabrata	7 (3.7)	6 (6.0)	13 (4.5)
C. glabrata + C. tropicalis	0	1 (1.0)	1 (0.3)
C. krusei	0	1 (1.0)	1 (0.3)
C. parapsilosis	1 (0.5)	0	1 (0.3)
C. tropicalis	4 (2.1)	0	4 (1.4)
Saccharomyces sp.	1 (0.5)	0	1 (0.3)
Baseline VSS score			
Mean (sd)	9.6 (2.5)	9.5 (2.7)	9.6 (2.5)
Median	9	9	9
Min, Max	5, 18	4, 17	4, 18
History of VVC	6 (3.2)	3 (3.0)	9 (4.7)

Source: Reviewer conducted analyses using ADSL, ADFA, ADMB, and ADMH datasets

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance in the ITT population was high (98.7%). All but 5 subjects randomized to receive ibrexafungerp received both doses of study drug. As previously mentioned, two of these subjects did not take the second dose due to an adverse event. Both subjects received rescue medication with fluconazole at their early termination visit. For the other 3 subjects, it is not known if these subjects took the second dose since they discontinued the study after the first dose and did not return their diaries.

The use of concomitant medications was reported by 157 (82.6%) ibrexafungerp and 88 (88.0%) placebo subjects in the mITT population. Other than for triazole derivatives received as rescue therapy, the incidence and type of concomitant medications were generally comparable between treatment groups. Following triazole derivatives (primarily fluconazole), the most frequently used concomitant medications used were propionic acid derivatives (18.4% ibrexafungerp and 17.0% placebo) and fixed combinations of progestogens and estrogens (16.8% ibrexafungerp and 18.0% placebo).

If the subject experienced persistent or worsening or recurrence of VVC symptoms, rescue antifungal therapy was permitted. Rescue antifungal therapy medication use was lower for the ibrexafungerp group than the placebo group. At or prior to the TOC visit, 16.8% of ibrexafungerp subjects and 33% of placebo subjects in the mITT population received rescue antifungal medication. The most frequently used rescue antifungal medication was fluconazole in 50 (26.3%) ibrexafungerp and 42 (42.0%) placebo subjects.

Table 8-5: Use of Rescue Medications in Study 303 (mITT Population)

Timing of Rescue Medication	Ibrexafungerp (N=190) n (%)	Placebo (N=100) n (%)
At or prior to TOC	32 (16.8)	33 (33.0)
After TOC	22 (11.6)	14 (14.0)

Source: Reviewer conducted analysis using ADSL and ADCM datasets.

Efficacy Results-Primary Endpoint

Clinical outcome at the TOC visit (Day 8-14) for the mITT population is summarized in Table 8-6. The percentage of subjects with clinical cure (VSS score =0) is statistically significantly higher for the ibrexafungerp group compared to the placebo group (50% vs 28%, p=0.001). The difference between treatment groups was 22% with a 95% confidence interval of (10.2%, 32.8%).

Table 8-6: Clinical Cure at TOC Visit in Study 303 (mITT population)

Outcome	Ibrexafungerp (N=190) n (%)	Placebo (N=100) n (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Cure	95 (50.0)	28 (28.0)	1.70 (1.2, 2.5) 0.001	22.0 (10.2, 32.8)

Source: Adapted from Table 14.2.1.1.1.1 of response to information request submitted 12/11/20 and confirmed by reviewer using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test adjusted for site and diagnosis of diabetes
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

Clinical cure at TOC by various subgroups is summarized in Table 8-7 for the mITT population. Interpretation of these results must be made with caution given lack of type 1 error control for multiple analyses and the limited sample size in some of the subgroup categories. The difference between treatment groups in clinical cure rates at TOC was generally comparable for most subgroups and supportive of the overall population. Exceptions are those of Other race, those with a diagnosis of diabetes, and those with *C. glabrata* at baseline. However, the sample size of these subgroups is too limited to draw definitive conclusions regarding differences between the treatment groups.

Table 8-7: Clinical Cure at TOC for Various Subgroups in Study 303 (mITT population)

Subgroup	Ibrexafungerp n/N (%)	Placebo n/N (%)	Difference (95% CI)
Race			
White	49/103 (47.6)	13/55 (23.6)	23.9 (8.2, 37.7)
Black	40/74 (51.1)	14/43 (32.6)	21.5 (2.7, 38.4)
Asian	4/4 (100)	-	-
Other	2/9 (22.2)	1/2 (50.0)	-27.8 (-77.5, 30.1)
Age (years)			
< 18	-	0/1 (0.0)	-
18 to 35	55/108 (50.9)	16/56 (28.6)	22.3 (6.5, 36.5)
≥ 36	40/82 (48.8)	12/43 (27.9)	20.9 (2.7, 36.9)
Diabetes			
Yes	6/18 (33.3)	3/8 (37.5)	-4.2 (-43.1, 31.5)
No	89/172 (51.7)	25/92 (27.2)	24.6 (12.3, 35.7)
Body Mass Index			
≤35	71/146 (48.6)	20/77 (26.0)	22.7 (9.3, 34.7)

> 35	24/44 (54.6)	8/23 (34.8)	19.8 (-5.6, 42.0)
Baseline *Candida* species**			
C. albicans	88/175 (50.3)	25/92 (27.2)	23.1 (10.9, 34.3)
C. glabrata	4/11 (36.4)	3/11 (27.3)	9.1 (-29.9, 45.6)

Source: Reviewer conducted analyses using ADSL and ADEFF datasets
*Difference (ibrexafungerp-placebo) and 95% confidence interval is based on Miettinen and Nurminen's method
**Some subjects tested positive for more than 1 *Candida* species at baseline. The number of subjects with the specified *Candida* species at baseline regardless of whether another *Candida* species was also present at baseline is used as the denominator.

Efficacy Results-Secondary and Other Relevant Endpoints

The results for mycological eradication at TOC are summarized in Table 8-8. For the overall mITT population, the percentage of subjects with mycological eradication at the TOC visit was statistically significantly higher for the ibrexafungerp group than the placebo group (49.5% vs 19%). The results are similar for subjects who tested positive for *C. albicans* at baseline, as the majority of the subjects had *C. albicans* at baseline. For subjects who tested positive for *C. glabrata* at baseline, mycological persistence was noted in all but 2 subjects, both in the placebo group. Although the 11 ibrexafungerp subjects who tested positive for *C. glabrata* at baseline were all persistent at TOC, 4 of the 11 were considered clinical cures (Table 8-7) and only 3 subjects required rescue antifungal treatment (2 at the TOC visit and 1 at the FU visit).

Table 8-8: Mycological Eradication at TOC Study 303 (mITT population)

	Ibrexafungerp n/N (%)	**Placebo** n/N (%)	**Relative Risk (95% CI)* p-value**	**Difference (95% CI)****
All subjects	94/190 (49.5)	19/100 (19.0)	2.9 (1.8, 4.7) <0.001	30.5 (19.4, 40.3)
Subjects with *C. albicans****	90/175 (51.4)	17/92 (18.5)	3.1 (1.9, 5.1) <0.001	33.0 (21.4, 43.1)
Subjects with *C. glabrata****	0/11 (0)	2/11 (18.2)	nc	-18.2 (-48.4, 11.2)

Source: Adapted from Table 14.2.1.2.1.1 of response to information request submitted 12/11/20 and reviewer conducted analysis using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test adjusted for site and diagnosis of diabetes
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method
***Some subjects tested positive for more than 1 *Candida* species at baseline. The number of subjects with the specified *Candida* species at baseline regardless of whether another *Candida* species was also present at baseline is used as the denominator.

The results of overall success at TOC are summarized in Table 8-9. A subject was an overall success at TOC if at TOC she was a clinical cure and had mycological eradication. The percentage of subjects with overall success at TOC was significantly greater for ibrexafungerp (33.7%) compared to placebo (12.0%) with a difference of 21.7% in favor of ibrexafungerp.

Table 8-9: Overall Success at TOC Study 303 (mITT population)

Outcome	Ibrexafungerp N=190 n (%)	Placebo N=100 n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Overall Success at EOT	64 (33.7)	12 (12.0)	3.1 (1.7, 5.6) <0.001	21.7 (11.8, 30.6)

Source: Reviewer conducted analysis using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test adjusted for site and diagnosis of diabetes
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

Clinical cure required the complete resolutions of all signs and symptoms (VSS score=0). Clinical improvement was defined to allowed for subjects to have a VSS score of 0 or 1, as a single symptom with mild severity was felt to also represent a clinically acceptable response for the subject. The percentage of subjects with clinical improvement at TOC in the mITT population was statistically significantly greater for ibrexafungerp (64.2%) compared to placebo (36.0%) with a difference of 28.2% in favor of ibrexafungerp. As seen in Table 8-10, most of the subjects who met the definition of clinical improvement had a VSS score=0 and although there is a numerical difference between treatment groups for those with a VSS score=1, most of the difference observed is attributed to subjects having a VSS score=0.

Table 8-10: Clinical Improvement at TOC Study 303 (mITT population)

Outcome	Ibrexafungerp N=190 n (%)	Placebo N=100 n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Clinical Improvement at EOT	122 (64.2)	36 (36.0)	1.7 (1.3, 2.4)	28.2 (16.2, 39.3)
VSS score =0	95 (50.0)	28 (28.0)	<0.001	
VSS score=1	27 (14.2)	8 (8.0)		

Source: Adapted from Table 14.2.1.5.1 of response to information request submitted 12/11/20 and reviewer conducted analysis using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test adjusted for site and diagnosis of diabetes
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

The results for clinical cure at FU (Day 21-29) are summarized in Table 8-11. For the mITT population, the percentage of subjects with clinical cure at FU was 59.5% for ibrexafungerp and 44.0% for placebo with a difference between treatment groups of 15.5%. While the difference between treatment groups at FU is less than that observed at TOC (Table 8-6), it remains nominally statistically significant in favor of ibrexafungerp.

Table 8-11: Clinical Cure at FU Study 303 (mITT population)

Outcome	Ibrexafungerp N=190 n (%)	Placebo N=100 n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Clinical Cure at FU	113 (59.5)	44 (44.0)	1.4 (1.1, 1.9) 0.007	15.5 (3.4 27.1)

Source: Reviewer conducted analysis using ADEFF dataset

*Relative risk, 95% confidence interval, and p-value from CMH test adjusted for site and diagnosis of diabetes
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

8.1.2. Study SCY-078-306

Trial Design

Study 306 was a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of ibrexafungerp compared to placebo in the treatment of female subjects 12 years and older with acute vulvovaginal candidiasis (VVC). The study design including inclusion/exclusion criteria, treatments administered, and study visits were identical to that of Study 303. Refer to Section 8.1.1 **Trial Design** for details. In addition to sites in the United States (19 sites), Study 306 also included sites in Bulgaria (18 sites). The study was started on June 7, 2019 and completed on February 7, 2020.

Study Endpoints

The primary and secondary endpoints were the same as Study 303. Refer to Section 8.1.1 **Study Endpoints** for details.

Statistical Analysis Plan

The SAP was finalized on March 24, 2020 prior to database lock.

Analysis Populations

The ITT population includes all randomized subjects who signed the informed consent form and received at least one dose of study drug.

The modified ITT (mITT) population includes all randomized subjects who had a positive culture for *Candida* species at baseline and received at least one dose of study drug.

The per-protocol (PP) population includes all mITT subjects who completed study drug treatment, had a TOC (or early termination TOC) evaluation that included documentation of signs, symptoms, and collection of a vaginal culture, and had no major protocol deviation.

The primary analysis population for efficacy is the mITT population. The ITT and PP populations were considered supportive.

The safety set includes all subjects randomly assigned to receive study drug who received at least one dose of study drug and had at least one postbaseline evaluation.

Reviewer's Comment: *The clinical study report for Study 306, indicated a change in the definition of the mITT population used in the clinical study report from that stated in the SAP for Study 306. The definition of the mITT population used in the clinical study report was all randomized subjects who had a positive culture for Candida species at baseline, a diagnosis of*

symptomatic AVVC as defined in Inclusion Criterion 2 at baseline, and received at least one dose of study drug. Inclusion criterion 2 is:

Subject had a diagnosis of symptomatic AVVC that met the following criteria:

a) Minimum composite vulvovaginal signs and symptoms score of ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater on the Vulvovaginal Signs and Symptoms (VSS) scale at baseline

b) Positive microscopic examination with 10% KOH in a vaginal sample collected at screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts

c) Normal vaginal pH (≤4.5)

The Applicant indicated the exclusion of subjects without a diagnosis of symptomatic VVC at baseline was deemed in line with ICH E9 that indicates that the failure to satisfy major entry criteria is one of a limited number of circumstances that could lead to excluding randomized subjects from a full analysis set (similar to the mITT population in Study 306). While this is an accurate statement, it has not been the Division's practice to exclude subjects from the mITT population unless the reason for not meeting an entry criterion was due to not receiving lab results for samples taken prior to randomization until after the start of treatment. Since culture results are typically not known until after randomization, the Division has allowed for the exclusion of subjects with a negative culture for Candida from the mITT in VVC treatment trials. However, whether a subject is symptomatic should be known at the baseline visit and prior to continuing with randomization. Therefore, the Division does not agree with change in the definition of the mITT population from that stated in the SAP applied in the clinical study report.

As previously mentioned, the Applicant was asked to revise the mITT population to be based on the definition stated in the SAP, update the ADSL dataset to include a flag for this population, and rerun the primary efficacy analyses based on this population. All discussions and tables presented regarding the mITT population are based on the SAP-stated definition.

Analysis Methods

The primary analysis was a comparison of the proportion of subjects with clinical cure at the TOC visit in the ibrexafungerp group versus the placebo group. A Cochran-Mantel-Haenszel (CMH) test adjusted for country and diabetes mellitus diagnosis was conducted to assess the statistical significance of the difference between treatment groups. The p-value, relative risk and 95% confidence interval were calculated. Additionally, this reviewer calculated the difference in proportions (ibrexafungerp – placebo) and corresponding 95% confidence interval based on the method of Miettinen and Nurminen.

The secondary endpoints were analyzed using same methods as the primary endpoint. For the categorical endpoints (primary and secondary), missing responses were imputed as non-responders (failures, mycological persistence) in the analyses.

Reviewer's Comment: *It should be noted that the SAP for Study 306 added the stratification factor of diabetes mellitus diagnosis (yes/no) and country (US/Bulgaria) as factors in the efficacy analyses modelled.*

Sample Size Calculation

Assuming clinical cure rates at TOC of 50% for ibrexafungerp and 30% for placebo and a 2:1 randomization, approximately 282 subjects were expected to provide 90% power to detect a difference between the treatment groups with a type 1 error rate of 5%. It was initially assumed that approximately 20% of subjects would not have a mycological culture-confirmed infection at baseline. Therefore, the samples size was increased by 72 subjects for a total of 354 subjects (244 subjects randomized to ibrexafungerp and 122 subjects randomized to placebo).

However, during the trial it was noted that the rate of "no growth" samples was higher than anticipated. Therefore, the protocol was amended to allow for additional subjects to be recruited to ensure approximately 282 evaluable subjects (i.e. culture positive) are accrued with an expected maximum of 470 subjects.

Reviewer's Comment: *Since the change in sample size was to ensure a sufficient number of evaluable subjects (i.e., those with a positive culture which make up the primary analysis population), the change was deemed acceptable by the Division and not to impact the integrity of the trial.*

Interim Analysis

No interim analysis of efficacy data was conducted.

Protocol Amendments

The original protocol was dated November 20, 2018. There was one protocol amendment dated October 23, 2019. The primary change in the amendment was to revise the sample size for the study. See discussion under Sample Size Calculation.

There was also a protocol addendum specific to Bulgaria dated April 16, 2019 which restricted eligible subjects to those 18 years and older.

Study Results

Compliance with Good Clinical Practices

The Applicant states that "The study was conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Council for Harmonisation (ICH) tripartite guideline E6: Good Clinical Practice (GCP) guidelines, the US Code of Federal Regulations sections that address

clinical research studies, applicable European Union regulations, and/or other national and local ethical and legal requirements, as applicable".

Financial Disclosure

The Applicant certified that they had not entered into any financial arrangements with the clinical investigators in Study 306 whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), the investigators did not have any proprietary interest in the product or significant interest in the trial sponsor, and the clinical investigators were not recipients of significant payments of other sorts.

Patient Disposition

A total of 455 subjects were randomized in the study. Six subjects (5 ibrexafungerp and 1 placebo) did not receive any study medication and were excluded from all efficacy and safety analyses. All treated subjects received the treatment to which they were randomized. Therefore, the ITT and the Safety populations are the same and include 298 ibrexafungerp subjects and 151 placebo subjects. A total of 109 (36.5%) ibrexafungerp subjects and 62 (41.1%) placebo subjects did not have yeast isolated at baseline and were excluded from the mITT population. The per-protocol population excluded an additional 11 ibrexafungerp subjects and 12 placebo subjects for protocol deviations. The analysis populations are summarized in Table 8-12.

Table 8-12: Analysis Populations for Study 306

Analysis Population	Ibrexafungerp N (%)	Placebo N (%)	Total N (%)
Randomized	303 (100)	152 (100)	455 (100)
ITT/Safety*	298 (98.3)	151 (99.3)	449 (98.7)
mITT**	189 (63.4)	89 (58.9)	278 (61.9)
Per-protocol**	178 (59.7)	77 (51.0)	255 (56.8)

Source: Reviewer conducted analysis using ADSL dataset
*% of randomized subjects
**% of ITT population

In the ITT population, a total of 4 subjects (2 in each treatment group) did not complete treatment. The 2 ibrexafungerp subjects did not take the second dose due to an adverse event. The 2 placebo subjects withdrew from the study and did not return their diaries, therefore receipt of the second dose could not be verified.

A total of 246 (82.6%) ibrexafungerp subjects and 102 (67.5%) placebo subjects in the ITT population completed the study. The primary reason for premature discontinuation from the study was lack of efficacy and/or use of antifungal therapy prior to or at the TOC visit. A higher percentage of placebo subjects (27.2%) compared to ibrexafungerp subjects (13.4%) discontinued for this reason. Three ibrexafungerp subjects (1.0%) compared to no placebo

subjects discontinued the study due to an adverse event. Subject disposition including the reason for discontinuing treatment and the study are summarized in Table 8-13.

Table 8-13: Subject Disposition in Study 306 (ITT Population)

	Ibrexafungerp (N=298) n (%)	**Placebo** (N=151) n (%)
Completed Treatment	296 (99.3)	149 (98.7)
Discontinued Treatment	2 (0.7)	2 (1.3)
Adverse event	2 (0.7)	2 (1.3)
Lost to follow-up/Patient withdrawal	0	0
Completed Study	246 (82.6)	102 (67.5)
Discontinued Study	52 (17.4)	49 (32.5)
Lack of efficacy and/or use of antifungal therapy prior to TOC	40 (13.4)	41 (27.2)
Use of antifungal therapy after TOC	3 (1.0)	0
Adverse event	3 (1.0)	0
Lost to follow-up	1 (0.3)	2 (1.3)
Physician Decision	0	1 (0.7)
Pregnancy	1 (0.3)	0
Withdrawal by Subject	2 (0.7)	0
Other	2 (0.7)	5 (3.3)

Source: Adapted from Tables 5-1 and 5-11 of Study 306 Clinical Study Report and confirmed by Reviewer using ADSL dataset

Protocol Violations/Deviations

Major protocol deviations in the ITT population are summarized in Table 8-14. At least 1 major protocol deviation was reported for 9 (3.0%) ibrexafungerp subjects and 9 (6.0%) placebo subjects. One placebo subject had 3 major protocol deviations. For both treatment groups, the most commonly reported major protocol deviations were due not meeting inclusion/exclusion criteria. The reported protocol deviations are not expected to have had an impact on safety or efficacy analyses and the overall study results.

Table 8-14: Major Protocol Deviations in Study 306 (ITT Population)

Category	**Ibrexafungerp** (N=298) n (%)	**Placebo** (N=151) n (%)
At least 1 major protocol deviation	9 (3.0)	9 (6.0)
Inclusion/Exclusion Criteria	4 (1.3)	8 (5.3)
Study procedures/assessments	2 (0.7)	1 (0.7)
Study treatment compliance	3 (1.0)	2 (1.3)

Source: Adapted from Table 5-3 of Study 306 Clinical Study Report
Note: 1 placebo subject had more than one major protocol deviation

Demographic and Other Baseline Characteristics

Table 8-15 summarizes demographic and baseline characteristics of subjects in the mITT population. There were no significant differences between the treatment groups. Approximately 80% of the subjects were White and 19% were Black. The median age was 32 years and the majority were in the 18 to 35 years age group. Although enrollment was open to adolescents at the sites in the United States, no subjects less than 18 years were enrolled. The median body mass index was 24.3 and approximately 45% of the subjects were classified as normal weight. Less than 5% of subjects were diabetic. The majority of the subjects were from Bulgaria (61.2%) and the remaining were from the United States (38.8%)

C. albicans was the most commonly identified species at baseline (n=166 or 87.8% for ibrexafungerp and n=81 or 91% for placebo) followed by *C. glabrata* (n=20 or 10.6% for ibrexafungerp and n=8 or 9.0% for placebo). Eleven ibrexafungerp subjects and 5 placebo subjects had mixed infections of *C. albicans* with another *Candida* species. The median composite VSS score at baseline was 10 and ranged from 4 to 18. Few subjects reported having a history of VVC (3.7% for ibrexafungerp and 6.7% for placebo).

Table 8-15: Demographic Characteristics in Study 306 (mITT population)

Parameter	**Ibrexafungerp** (N=189) n (%)	**Placebo** (N=89) n (%)	**Total** (N=278) n (%)
Sex			
Female	189 (100)	89 (100)	278 (100)
Race			
White	154 (81.5)	70 (78.7)	224 (80.6)
Black	34 (18.0)	19 (21.3)	53 (19.1)
Other	1 (0.5)	0	1 (0.4)
Ethnicity			
Hispanic	22 (11.6)	6 (6.7)	28 (10.1)
Not Hispanic	167 (88.4)	83 (93.3)	250 (89.9)
Age (years)			
Mean (sd)	33.7 (10.3)	33.7 (10.6)	33.7 (10.4)
Median	32	32	32
Min, Max	18, 65	18, 65	18, 65
18 to 35	118 (62.4)	56 (62.9)	174 (62.6)
36 to 49	56 (29.6)	27 (30.3)	83 (29.9)
50 to 64	14 (7.4)	5 (5.6)	19 (6.8)
≥ 65	1 (0.5)	1 (1.1)	2 (0.7)
Body Mass Index (kg/m^2)			
Mean (sd)	25.5 (7.1)	27.3 (8.4)	26.1 (7.6)
Median	24.1	24.6	24.3
Min, Max	15.4, 58.8	17.4, 55.1	15.4, 58.8
Underweight (<18.5)	18 (9.5)	8 (9.0)	26 (9.4)
Normal (18.5-<25)	88 (46.6)	37 (41.6)	125 (45.0)
Overweight (25-<30)	42 (22.2)	19 (21.4)	61 (21.9)
Obese (30-<40)	33 (17.5)	13 (14.6)	46 (16.5)
Morbidly obese (≥40)	8 (4.2)	12 (13.5)	20 (7.2)

Diabetes Mellitus			
Yes	8 (4.2)	5 (5.6)	13 (4.7)
No	181 (95.8)	84 (94.4)	265 (95.3)
Country			
United States	67 (35.5)	41 (46.1)	108 (38.8)
Bulgaria	122 (64.5)	48 (53.9)	170 (61.2)
***Candida* species at baseline**			
C. albicans	155 (82.0)	76 (85.4)	231 (83.1)
C. albicans + C. glabrata	6 (3.2)	3 (3.4)	9 (3.2)
C. albicans +C. kefyr	2 (1.1)	0	2 (0.7)
C. albicans +C. parapsilosis	2 (1.1)	0	2 (0.7)
C. albicans +C. tropicalis	1 (0.5)	2 (2.2)	3 (1.1)
C. dubliniensis	0	1 (1.1)	1 (0.4)
C. glabrata	14 (7.4)	5 (5.6)	19 (6.8)
C. inconspicua	1 (0.5)	0	1 (0.4)
C. kefyr	1 (0.5)	1 (1.1)	2 (0.7)
C. krusei	2 (1.1)	0	2 (0.7)
C. lusitaniae	1 (0.5)	0	1 (0.4)
C. norvegensis	1 (0.5)	0	1 (0.4)
C. parapsilosis	1 (0.5)	0	1 (0.4)
C. tropicalis	2 (1.1)	1 (1.1)	3 (1.1)
Baseline VSS score			
Mean (sd)	10.3 (2.7)	9.5 (2.8)	
Median	10	10	10
Min, Max	4, 18	4, 18	4, 18
History of VVC	7 (3.7)	6 (6.7)	13 (4.7)

Source: Reviewer conducted analyses using ADSL, ADFA, ADMB, and ADMH datasets

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance in the ITT population was high (98.7%). All but 5 subjects (3 ibrexafungerp and 2 placebo) received both doses of study drug. As previously mentioned, two ibrexafungerp subjects did not take the second dose due to an adverse event. The third ibrexafungerp subject mistakenly only took 1 tablet per dose rather than 2 tablets per dose. All three of these subjects completed the study without need for additional antifungal therapy. For the two placebo subjects, it is not known if these subjects took the second dose since they discontinued the study after the first dose and did not return their diaries.

In the mITT population, the use of concomitant medications was reported by 102 (54.0%) ibrexafungerp and 64 (71.9%) placebo subjects. Other than for triazole and imidazole derivatives received as rescue therapy, the incidence and type of concomitant medications were generally comparable between treatment groups. Following triazole derivatives (primarily fluconazole), the most frequently used concomitant medications used were fixed combinations of progestogens and estrogens (9% of ibrexafungerp and 13.5% of placebo subjects).

If the subject experienced persistent or worsening or recurrence of VVC symptoms, rescue antifungal therapy was permitted. At or prior to the TOC visit, rescue antifungal therapy was

medication use was lower for the ibrexafungerp group (12.6%) than the placebo group (33.7%). However, after the TOC visit more ibrexafungerp subjects (5.8%) than placebo subjects (2.2%) received rescue antifungal therapy. The most frequently used rescue antifungal medication was fluconazole in 29 (15.3%) ibrexafungerp subjects and 30 (33.7%) placebo subjects.

Table 8-16: Use of Rescue Medications in Study 306 (mITT Population)

Timing of Rescue Medication	Ibrexafungerp (N=189) n (%)	Placebo (N=89) n (%)
At or prior to TOC	24 (12.6)	30 (33.7)
After TOC	11 (5.8)	2 (2.2)

Source: Reviewer conducted analysis using ADSL and ADCM datasets.

Efficacy Results – Primary Endpoint

Clinical cure at the TOC visit for the mITT population is summarized in Table 8-17. Overall, the percentage of subjects with clinical cure (VSS score =0) is statistically significantly higher for the ibrexafungerp group compared to the placebo group (63.5% vs 44.9%, p=0.009). The difference between treatment groups is 18.6% with a 95% confidence interval of (6.0%, 30.6%). The results are also summarized by country. The clinical cure rates observed in Bulgaria for both treatment groups are higher than the clinical cure rates observed in the United States. In both countries, the clinical cure rate for ibrexafungerp was higher than for placebo. However, the difference between treatment groups was not as large for Bulgaria as the United States.

Table 8-17: Clinical Cure at TOC Visit in Study 306 (mITT population)

Parameter	Ibrexafungerp n/N (%)	Placebo n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Overall	120/189 (63.5)	40/89 (44.9)	1.35 (1.06, 1.73) 0.009	18.6 (6.0, 30.6)
United States	37/67 (55.2)	13/41 (31.7)	1.71 (1.05, 2.278) 0.02	23.5 (4.1, 40.8)
Bulgaria	83/122 (68.0)	27/48 (56.3)	1.21 (0.92, 1.60) 0.151	11.8 (-4.0, 28.0)

Source: Adapted from Tables 14.2.1.1.1.1, 14.2.1.1.1.7, and 14.2.1.1.1.8 for Study 306 of response to information request submitted 12/11/20 and reviewer conducted analyses using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test for overall is adjusted for country and diabetes diagnosis and for each country adjusted for diabetes diagnosis
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

Clinical cure at TOC by various subgroups is summarized in Table 8-18 for the mITT population. Interpretation of these results must be made with caution given lack of type 1 error control for multiple analyses and the limited sample size in some of the subgroup categories. The difference between treatment groups in clinical cure rates at TOC were generally comparable for most subgroups and supportive of the overall population. It should be noted that all Black subjects and all but 2 subjects with a BMI > 35 (1 in each treatment group) were from the

United States. However, the small sample size of these subgroups as well as those with a diagnosis of diabetes and those with *C. glabrata* at baseline limits the ability to draw definitive conclusions regarding any or lack of difference.

Table 8-18: Clinical Cure at TOC for Various Subgroups in Study 306 (mITT population)

Subgroup	Ibrexafungerp n/N (%)	Placebo n/N (%)	Difference (95% CI)
Race			
White	103/154 (66.9)	33/70 (47.1)	19.7 (5.7, 33.1)
Black	16/34 (47.1)	7/19 (36.8)	10.2 (-17.3, 35.5)
Other	1/1	-	-
Age (years)			
18 to 35	72/118 (61.0)	22/56 (39.3)	21.7 (5.9,36.5)
≥ 36	48/71 (67.6)	18/33 (54.6)	13.1 (-6.9, 32.5)
Diabetes			
Yes	4/8 (50.0)	1/5 (20.0)	30.0 (-26.1, 68.6)
No	116/181 (64.1)	39/84 (46.4)	17.7 (4.8, 30.1)
Body Mass Index			
≤35	114/168 (67.9)	34/72 (47.2)	20.6 (7.0, 33.7)
> 35	6/21 (28.6)	6/17 (35.3)	-6.7 (-35.1, 22.3)
Baseline *Candida* species**			
C. albicans	108/166 (65.1)	38/81 (46.9)	18.2 (5.0, 30.9)
C. glabrata	11/20 (55.0)	2/8 (25.0)	30.0 (-11.5, 59.5)

Source: Reviewer conducted analyses using ADSL and ADEFF dataset
*Difference (ibrexafungerp-placebo) and 95% confidence interval is based on Miettinen and Nurminen's method
**Some subjects tested positive for more than 1 *Candida* species at baseline. The number of subjects with the specified *Candida* species at baseline regardless of whether another *Candida* species was also present at baseline is used as the denominator.

Efficacy Results – Secondary and other relevant endpoints

The results for mycological eradication at TOC are summarized in Table 8-19. For the overall mITT population, the percentage of subjects with mycological eradication at the TOC visit was higher for the ibrexafungerp group than the placebo group (58.7% vs 29.2%). The results are similar for subjects who tested positive for *C. albicans* at baseline, as the majority of the subjects had *C. albicans* at baseline. Mycological eradication was lower for subjects who tested positive for *C. glabrata* at baseline. As seen with clinical cure at TOC, mycological eradication rates observed in Bulgaria for both treatment groups are higher than the mycological eradication rates observed in the United States. In both countries, the mycological eradication rate for ibrexafungerp was higher than for placebo. However, the difference between treatment groups was not as large for Bulgaria as the United States.

Table 8-19: Mycological Eradication at TOC Study 306 (mITT population)

	Ibrexafungerp n/N (%)	Placebo n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
All subjects	111/189 (58.7)	26/89 (29.2)	1.86 (1.34, 2.57)	29.5 (17.2, 40.6)

			<0.001	
United States	29/67 (43.3)	3/41 (7.3)	5.99 (1.87, 19.21) <0.001	36.0 (20.1, 49.5)
Bulgaria	82/122 (67.2)	23/48 (47.9)	1.40 (1.02, 1.93) 0.020	19.3 (2.9, 35.1)
Subjects with *C. albicans****	108/166 (65.1)	24/81 (29.6)	2.02 (1.46, 2.81) <0.001	35.4 (22.5, 46.9)
Subjects with *C. glabrata****	4/20 (20.0)	1/8 (12.5)	1.81 (0.24, 13.51) 0.559	7.5 (-30.8, 33.6)

Source: Adapted from Tables 14.2.1.2.1.1, 14.2.1.2.1.4, and 14.2.1.2.1.5 for Study 306 of response to information request submitted 12/11/20 and reviewer conducted analyses using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test for overall is adjusted for country and diabetes diagnosis and for each country adjusted for diabetes diagnosis
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method
***Some subjects tested positive for more than 1 *Candida* species at baseline. The number of subjects with the specified *Candida* species at baseline regardless of whether another *Candida* species was also present at baseline is used as the denominator.

The results for overall success at TOC are summarized in Table 8-20. A subject was an overall success at TOC if at TOC she was a clinical cure and had mycological eradication. Overall, the percentage of subjects with overall success at TOC was nominally significantly greater for ibrexafungerp (43.9%) compared to placebo (27.0%) with a difference of 16.9% in favor of ibrexafungerp. As expected, since seen for clinical cure and mycological eradication at TOC, overall success rates at TOC observed in Bulgaria for both treatment groups are higher than the overall success rates observed in the United States. In both countries, the overall success rate at TOC for ibrexafungerp was higher than for placebo. However, the difference between treatment groups was not as large for Bulgaria as the United States.

Table 8-20: Overall Success at TOC Study 306 (mITT population)

Parameter	**Ibrexafungerp** n/N (%)	**Placebo** n/N (%)	**Relative Risk (95% CI)*** **p-value**	**Difference (95% CI)****
Overall	83/189 (43.9)	24/89 (27.0)	1.5 (1.0, 2.1) 0.022	16.9 (4.8, 28.0)
United States	19/67 (28.4)	2/41 (4.9)	5.7 (1.4, 23.0) 0.003	23.5 (9.4, 36.3)
Bulgaria	64/122 (52.5)	22/48 (45.8)	1.1 (0.8, 1.6) 0.440	6.6 (-10.0, 22.7)

Source: Reviewer conducted analyses using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test for overall is adjusted for country and diabetes diagnosis and for each country adjusted for diabetes diagnosis
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

Clinical cure required the complete resolutions of all signs and symptoms (VSS score=0). Clinical improvement was defined to allow for subjects to have a VSS score of 0 or 1, as a single symptom with mild severity was felt to also represent a clinically acceptable response for the subject. The percentage of subjects with clinical improvement at TOC in the overall mITT

population was statistically significantly greater for ibrexafungerp (72.5%) compared to placebo (55.1%) with a difference of 17.4% in favor of ibrexafungerp. As seen in Table 8-21, most of the subjects who met the definition of clinical improvement had a VSS score=0 and relatively few subjects in either treatment had a VSS score =1. Therefore, the difference observed is attributed to subjects having a VSS score=0.

Table 8-21: Clinical Improvement at TOC Study 306 (mITT population)

Outcome	Ibrexafungerp n/N (%)	Placebo n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Overall	137/189 (72.5)	49/89 (55.1)	1.2 (1.0, 1.6)	17.4 (5.4, 29.5)
VSS score =0	120 (63.5)	40 (44.9)	0.010	
VSS score=1	17 (9.0)	9 (10.1)		
United States	43/67 (64.2)	18/41 (43.9)	1.4 (1.0, 2.1)	20.3 (0.9, 38.4)
VSS score =0	37 (55.2)	13 (31.7)	0.044	
VSS score=1	6 (9.0)	5 (12.2)		
Bulgaria	94/122 (77.1)	31/48 (64.6)	1.2 (0.9, 1.5)	12.5 (-2.2, 28.3)
VSS score =0	83 (68.0)	27 (56.3)	0.100	
VSS score=1	11 (9.0)	4 (8.3)		

Source: Adapted from Tables 14.2.1.5.1, 14.2.1.5.5, and 14.2.1.5.6 for Study 306 of response to information request submitted 12/11/20 and reviewer conducted analyses using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test for overall is adjusted for country and diabetes diagnosis and for each country adjusted for diabetes diagnosis
**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

The results for clinical cure at FU are summarized in Table 8-22. For the overall mITT population, the percentage of subjects with clinical cure at FU was 72.5% for ibrexafungerp and 49.4% for placebo with a difference between treatment groups of 23.1%. As seen with clinical cure at TOC (Table 8-17), clinical cure rates at FU observed in Bulgaria for both treatment groups are higher than the clinical cure rates at FU observed in the United States. In both countries, the clinical cure rate at FU for ibrexafungerp was higher than for placebo but the difference between treatment groups was not as large for Bulgaria as the United States. Overall and for both countries, the clinical cure rates and difference in clinical cure rates between treatment groups at FU is increased from that observed at TOC.

Table 8-22: Clinical Cure at FU Study 306 (mITT population)

Parameter	Ibrexafungerp n/N (%)	Placebo n/N (%)	Relative Risk (95% CI)* p-value	Difference (95% CI)**
Overall	137/189 (72.5)	44/89 (49.4)	1.4 (1.1, 1.7) 0.006	23.1 (10.8, 35.0)
United States	41/67 (61.2)	14/41 (34.2)	1.8 (1.1, 2.8) 0.007	27.1 (7.6, 44.3)
Bulgaria	96/122 (78.7)	30/48 (62.5)	1.3 (1.0, 1.6) 0.031	16.2 (1.4, 32.0)

Source: Reviewer conducted analyses using ADEFF dataset
*Relative risk, 95% confidence interval, and p-value from CMH test for overall is adjusted for country and diabetes diagnosis and for each country adjusted for diabetes diagnosis

**Difference (ibrexafungerp- placebo) and 95% confidence interval is based on Miettinen and Nurminen's method

8.1.3. Assessment of Efficacy Across Trials

Two Phase 3 trials, Studies 303 and 306, were conducted to demonstrate the efficacy of ibrexafungerp for the treatment of VVC. The trials were identically designed, double-blind multicenter, randomized placebo-controlled studies. Study 303 was conducted solely in the United States. Study 306 was conducted in the United States and Bulgaria.

Primary Endpoint

The primary endpoint for both trials was clinical cure (complete resolution of vaginal signs and symptoms) at the TOC visit (Day 8-14) in the mITT population. A primary assessment of clinical cure at Day 8-14 is as recommended in the guidance for industry for the development of drugs for the treatment of VVC for products of a single day duration.

For both trials, the percentage of subjects with clinical cure at the TOC visit in the mITT population was significantly higher for ibrexafungerp than placebo. The rates observed for both treatment groups overall were higher in Study 306 than those observed in Study 303. In Study 306, the clinical cure rates at TOC observed in Bulgaria for both treatment groups are higher than the clinical cure rates observed in the United States and the difference between treatment groups was not as large for Bulgaria as the United States. However, the United States population in Study 306 had comparable response rates to Study 303 which was conducted solely in the United States.

Table 8-23: Clinical Cure at TOC Study 303 and 306 (mITT population)

Parameter	Study 303		Study 306	
	Ibrexafungerp n/N (%)	Placebo n/N (%)	Ibrexafungerp n/N (%)	Placebo n/N (%)
Overall	95/190 (50.0)	28/100 (28.0)	120/189 (63.5)	40/89 (44.9)
RR (95% CI)	1.70 (1.2, 2.5)		1.35 (1.06, 1.73)	
p-value	0.001		0.009	
Difference (95% CI)	22.0 (10.2, 32.8)		18.6 (6.0, 30.6)	
United States	95/190 (50.0)	28/100 (28.0)	37/67 (55.2)	13/41 (31.7)
RR (95% CI)	1.70 (1.2, 2.5)		1.71 (1.05, 2.278)	
p-value	0.001		0.02	
Difference (95% CI)	22.0 (10.2, 32.8)		23.5 (4.1, 40.8)	
Bulgaria	N/A		83/122 (68.0)	27/48 (56.3)
RR (95% CI)			1.21 (0.92, 1.60)	
p-value			0.151	
Difference (95% CI)			11.8 (-4.0, 28.0)	

Source: Table 8-6 and Table 8-17 of this review

Secondary and Other Endpoints

Secondary endpoints included mycological eradication at TOC, overall success at TOC (clinical cure and mycological eradication), clinical improvement at TOC (VSS score= 0 or 1), and clinical cure at FU. The results for these endpoints are summarized in Table 8-24 for each of the Phase 3 trials. P-values along with the difference in proportions and corresponding 95% confidence interval are reported for descriptive purposes only as there was no type-I error control for the secondary endpoints.

The interpretation of the results across the two trials for the secondary endpoints are consistent with those observed for the primary endpoint. For each endpoint, the percentage of subjects with the respective satisfactory response was nominally significantly higher for ibrexafungerp than for placebo. For both treatment arms, the rates observed in Study 306 are higher than those observed in Study 303. This is due to higher rates observed for Bulgaria in Study 306 than for the United States. However, the United States population in Study 306 had comparable response rates to Study 303 which was conducted solely in the United States (refer to Tables 8-19, 8-20, 8-21, and 8-22).

Table 8-24: Secondary Efficacy Endpoints Study 303 and 306 (mITT population)

Parameter	Study 303		Study 306	
	Ibrexafungerp n/N (%)	**Placebo** n/N (%)	**Ibrexafungerp** n/N (%)	**Placebo** n/N (%)
Mycological Eradication at TOC	94/190 (49.5)	19/100 (19.0)	111/189 (58.7)	26/89 (29.2)
RR (95% CI)	2.9 (1.8, 4.7)		1.86 (1.34, 2.57)	
p-value	<0.001		<0.001	
Difference (95% CI)	30.5 (19.4, 40.3)		29.5 (17.2, 40.6)	
Overall Success at TOC	64 (33.7)	12 (12.0)	83/189 (43.9)	24/89 (27.0)
RR (95% CI)	3.1 (1.7, 5.6)		1.5 (1.0, 2.1)	
p-value	<0.001		0.022	
Difference (95% CI)	21.7 (11.8, 30.6)		16.9 (4.8, 28.0)	
Clinical Improvement at TOC	122 (64.2)	36 (36.0)	137/189 (72.5)	49/89 (55.1)
RR (95% CI)	1.7 (1.3, 2.4)		1.2 (1.0, 1.6)	
p-value	<0.001		0.010	
Difference (95% CI)	28.2 (16.2, 39.3)		17.4 (5.4, 29.5)	
Clinical Cure at FU	113 (59.5)	44 (44.0)	137/189 (72.5)	44/89 (49.4)
RR (95% CI)	1.4 (1.1, 1.9)		1.4 (1.1, 1.7)	
p-value	0.007		0.006	
Difference (95% CI)	15.5 (3.4 27.1)		23.1 (10.8, 35.0)	

Source: Tables 8-8, 8-9, 8-10, 8-11, 8-19, 8-20, 8-21, and 8-22 of this review

8.1.4. Integrated Assessment of Effectiveness

The evidence to support the efficacy of ibrexafungerp for the treatment of VVC was primarily based on two identically designed, double-blind, multicenter, randomized, placebo-controlled Phase 3 studies, Study 303 and 306. Study 303 was conducted in the United States and Study 306 was conducted in the United States and Bulgaria.

The design of the studies followed the Guidance for Industry: Developing Drugs for the Treatment of Vulvovaginal Candidiasis. The primary endpoint was clinical cure (complete resolution of signs and symptoms, i.e. VSS score=0) assessed at the TOC visit (Day 8-14). Secondary endpoints included mycological eradication at TOC, overall response at TOC, and clinical cure at the FU visit (Day 21-29). The primary efficacy analysis population was the mITT population which included subjects with culture confirmed *Candida* infection at baseline who received at least 1 dose of study drug.

Both trials showed statistical superiority of ibrexafungerp over placebo in clinical cure at TOC in the mITT population. Across both treatment arms, the rates of clinical cure at TOC observed were higher in Study 306 than Study 303. This difference can be explained by where the studies were conducted. In Study 306, the clinical cure rates at TOC observed in Bulgaria for both treatment groups are higher than the clinical cure rates observed in the United States and the difference between treatment groups was not as large for Bulgaria as the United States. However, the United States population in Study 306 had comparable response rates to Study 303 which was conducted solely in the United States. The results for the secondary endpoints were consistent with the primary endpoint.

In Study 306, higher response rates for both treatment groups was consistently observed for Bulgaria as compared to the United States. Based on the data collected, no likely explanation for this difference was found. It is noted that there may be other cultural factors that can influence response rates in the United States as compared to Bulgaria. These differences are not highly concerning because of the following:

1. The analysis for Study 306 adjusts for the effect of country and the results were overall statistically significant.
2. The United States population in Study 306, which may be considered the most applicable population, had comparable response rates to Study 303 conducted solely in the United States.

The majority of subjects in both trials had culture-confirmed infection with *C. albicans.* Therefore, the results for subjects with *C. albicans* are consistent with the results for the overall mITT population. Less than 10% of subjects had culture-confirmed infection with *C. glabrata*. In general, subjects with *C. glabrata* had lower clinical cure rates and had mycological persistence at the TOC visit.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary safety analysis focused on the pooled data from two Phase 3 placebo-controlled trials of oral ibrexafungerp dosed at 300 mg PO BID for 1 day for treatment of acute VVC (VANISH-303 and VANISH-306). Two Phase 2 trials provided additional safety data in women treated for acute VVC with oral ibrexafungerp dosing regimens at total daily doses of 300-1250 mg and treatment durations of 1-5 days (SCY-078-203 and SCY-078-204). Safety data were also reviewed from 15 Phase 1 trials of healthy volunteers administered oral ibrexafungerp single

doses up to 1600 mg and repeat doses up to 800 mg daily for 28 days (with some studies also evaluating loading doses of 1250-1800 mg per day). Cardiac safety data were evaluated from a single Phase 1 trial of IV ibrexafungerp submitted in lieu of a TQT study (SCY-078-106). While not submitted as part of the safety database, summary safety data were also reviewed from ongoing trials using higher doses and/or longer durations of oral ibrexafungerp for other indications and from an adolescent PK study (SCY-078-120) evaluating oral ibrexafungerp 300 mg BID x 1 day that was completed after the NDA submission.

Findings from the pooled Phase 3 safety population of women who received at least one dose of study treatment are detailed in Section 8.2.4 *Safety Results*, with discussion of additional relevant safety data from the Phase 1 and Phase 2 trials. Data from the Phase 1 and Phase 2 safety analyses can be found in Section 16.5 *Clinical Appendix*.

The main safety issues identified during the development of ibrexafungerp were gastrointestinal adverse effects (gastric mucosal degeneration in nonclinical studies and frequent reports of diarrhea, abdominal pain, and nausea in clinical studies), increased transaminases (resulting in treatment discontinuation in a small number of subjects in early phase trials), hypersensitivity reactions (infrequent but requiring hospitalization in one subject), and thrombotic events (observed in an IV ibrexafungerp Phase 1 trial and resulting in a clinical hold of the IND). These issues are discussed in greater detail in Section 8.2.5 *Analysis of Submission-Specific Safety Issues*.

Animal studies identified a risk for fetal toxicity with oral ibrexafungerp exposure. Severe fetal malformations (including phocomelia and anencephaly) were observed when oral ibrexafungerp was administered to pregnant rabbits at 5-13x the recommended dose for VVC treatment. The animal embryo-fetal toxicity data are discussed in Section 5.5 *Toxicology* and the limited clinical data from women exposed to oral ibrexafungerp in early pregnancy are discussed in Section 8.2.9 *Additional Safety Explorations, Human Reproduction and Pregnancy.*

8.2.2. Review of the Safety Database

Overall Exposure

The oral ibrexafungerp safety database consists of 1067 subjects across 15 Phase 1 trials, 2 Phase 2 trials, and 2 Phase 3 trials (Table 8-25). There were 575 women exposed to the proposed oral ibrexafungerp dosing of 300 mg BID for one day, with most evaluated in the Phase 3 trials (n=545).

Table 8-25 Oral Ibrexafungerp Safety Population, Size and Denominators

Safety Database for Oral Ibrexafungerp **Individuals exposed to the study drug in this development program for the indication under review** **N=1067**					
Clinical Trial Groups	**Trial Name (Population)**	**Oral ibrexafungerp proposed dose 300 mg PO BID x 1 day**	**Oral ibrexafungerp other doses**	**Active control Fluconazole 150 mg PO x 1 dose**	**Placebo**
		(n= 575) [1]	**(n= 492)**	**(n= 64)**	**(n = 291)**
Controlled trials conducted for this indication	SCY-078-303/VANISH 303 (Healthy women with acute VVC)	247	0	0	124
	SCY-078-306/VANISH 306 (Healthy women with acute VVC)	298	0	0	151
All other than controlled trials conducted for this indication	SCY-078-204/DOVE Dose-finding study (Healthy women with moderate to severe VVC)	30	123 (150 mg BID, 300 mg BID, 450 mg BID, 750 mg daily x 1-3 days)	32	0
	SCY-078-203 Proof-of-concept study[2] (Healthy women with recurrent moderate to severe VVC)	0	64 (1250 mg Day 1 then 750 mg daily, x 2-4 days)	32	0
	SCY-078-001 Single dose PK/safety study (Healthy males)	0	16 (10 mg, 20 mg, 40 mg, 80 mg, 150 mg, 300 mg, 600 mg, 800 mg, 1600 mg x 1 dose)	0	0
	SCY-078-002 Multiple dose PK/safety study [also gastric histology] (Healthy males)	0	24 (300 mg, 600 mg, 800 mg daily x 10 days; 800 mg daily x 28 days)	0	8
	SCY-078-003 Single dose PK/safety study (Healthy elderly adults)	0	13 (500 mg x 1 dose)	0	4
	SCY-078-008 Single dose ketoconazole DDI study (Healthy males)	0	12 (50 mg x 1 dose)	0	2
	SCY-078-014 Multiple dose PK/safety study	0	6	0	2

	(Healthy males)		(600 mg TID x 1 day then 500 daily x 6 days)		
	SCY-078-015 Single dose pantoprazole DDI study with 2 formulations (Healthy males)	0	16 (500 mg x 1 dose)	0	0
	SCY-078-016 Multiple dose diltiazem DDI study (Healthy males)	0	16 (600 mg loading dose Day 1 then 100 mg daily x 13 days)	0	0
	SCY-078-102 Single dose formulation study (Healthy adults)	0	24 (500 mg x 1 dose)	0	0
	SCY-078-103 Multiple dose tacrolimus DDI study (Healthy males)	0	36 (1250 mg on Day 1 then 750 mg daily x 7 days)	0	0
	SCY-078-104 Multiple dose rosiglitazone DDI study (Healthy adults)	0	24 (1250 mg on Day 1 then 750 mg daily x 7 days)	0	0
	SCY-078-107 Single and multiple dose formulation study (Healthy adults)	0	32 (100 mg, 300 mg, 600 mg x 1 dose; 300 mg BID, 200 mg BID x 1 day)	0	0
	SCY-078-108 Multiple dose dabigatran DDI study (Healthy adults)	0	36 (750 mg BID x 2 days then 750 md daily x 2 days)	0	0
	SCY-078-111 Multiple dose safety/PK study (Healthy adults)	0	16 (750 mg BID x 2 days then 750 mg daily x 5 days)	0	0
	SCY-078-115 Multiple dose pravastatin DDI study (Healthy adults)	0	28 (750 mg BID x 2 days then 750 mg daily x 1 day)	0	0
	SCY-078-116 Single dose ADME study (Healthy males)	0	6 (300 mg x 1 dose)	0	0

Controlled trials conducted for other indications [3]			0	0	0

[1] Ten additional subjects were enrolled in a Phase 1 adolescent PK and safety study (SCY-078-120) and received oral ibrexafungerp 300 mg BID x 1 day. The study was completed during the review cycle and the Applicant submitted summary safety data. The final clinical study report will be submitted as a PMC.
[2]SCY-078-203 not included in the integrated safety summary (ISS) dataset, but individual study data submitted
[3]As of 31 July 2020, 258 additional subjects had received ibrexafungerp in ongoing clinical trials. Summary safety data were submitted from 144 women in SCY-078-304 (ongoing study of recurrent VVC) receiving the proposed ibrexafungerp dosing of 300 mg BID x 1 day (with dosing repeated every 4 weeks x 6 months). The remaining subjects were enrolled in trials for invasive fungal infections with different dosing regimens (1000-1500 mg loading dose, followed by 500-750 mg daily for 2-6wks) (b) (4)
Source: Clinical reviewer

0

Summary safety data were submitted from one ongoing, blinded, placebo-controlled trial of oral ibrexafungerp for prevention of recurrent VVC (SCY-078-304, 300 mg BID x 1 day, repeated every 4 weeks for 6 months). The NDA submission also referred to the 2020 Development Safety Update Report covering the reporting period from 24 February 2019 to 23 February 2020 (DSUR 05, IND 107521 SDN 0166) for data from ongoing trials of oral ibrexafungerp:

IND 107521 also contained the completed clinical study report from a Phase 2 pilot study of ibrexafungerp as oral-stepdown therapy for invasive candidiasis (SCY-078-202). There were 21 subjects in the safety analysis population treated for up to 28 days with oral ibrexafungerp 1000 mg loading dose then 500 mg daily (n=6), oral ibrexafungerp 1250 mg loading dose then 750 mg daily (n=7), oral fluconazole 800 mg loading dose then 400 mg daily (n=7), or IV micafungin 100 mg daily (n=1). The study did not have a pre-specified sample size, but rather planned to enroll enough subjects to allow preliminary characterization of safety and PK of oral ibrexafungerp compared to the standard of care in this population. The last study visit was completed 22 July 2016.

In response to an information request sent 17 February 2021, the Applicant submitted summary safety data from a PK study of adolescents (SCY-078-120) completed after the NDA submission. The study was not conducted under IND 107521. There were 10 adolescent females (age 12-17 y) enrolled and all received oral ibrexafungerp 300 mg BID x 1 day.

Relevant characteristics of the safety population

The pooled Phase 3 safety population consisted primarily of women aged 18-64 y (median age 33 y, range 17-76 y, Table 8-26). Five women > 65 y and no adolescents < 18 y received ibrexafungerp in the Phase 3 trials. The majority of subjects in the Phase 3 safety population were White (70%), 28% were Black/African American and 17% were Hispanic or Latino. Two-thirds of the subjects were enrolled in the U.S. and the remainder in Bulgaria.

Table 8-26 Demographic Characteristics – Pooled Phase 3 Safety Population

Subgroup	Oral ibrexafungerp 300 mg BID (N = 545) n (%)	Placebo BID (N = 275) n (%)	Total (N = 820) n (%)
Sex			
Female	545 (100.0)	275 (100.0)	820 (100.0)
Age			
Mean (SD)	34.2 (10.8)	35.1 (11.7)	34.5 (11.1)
Median (Min, Max)	33 (18, 76)	33 (17, 70)	33 (17, 76)
Age Group			
<18 y	0 (0.0)	1 (0.4)	1 (0.1)
18-64 y	540 (99.1)	269 (97.8)	809 (98.7)
>65 y	5 (0.9)	5 (1.8)	10 (1.2)
Race			
White	378 (69.4)	194 (70.5)	572 (69.8)
Black or African American	152 (27.9)	78 (28.4)	230 (28.0)
Asian	4 (0.7)	0 (0.0)	4 (0.5)
American Indian or Alaska Native	3 (0.6)	1 (0.4)	4 (0.5)
Other	8 (1.5)	2 (0.7)	10 (1.2)
Ethnicity			
Not Hispanic or Latino	445 (81.7)	236 (85.8)	681 (83.0)
Hispanic or Latino	100 (18.3)	39 (14.2)	139 (17.0)
Region			
United States	352 (64.6)	190 (69.1)	542 (66.1)
Europe[1]	193 (35.4)	85 (30.9)	278 (33.9)

[1]All were enrolled in Bulgaria.
Source: Clinical reviewer, OCS Demographics Tool V3

Other baseline characteristics of the pooled Phase 3 safety population are summarized in Table 8-27. The median body mass index was 26 kg/m^2 and > 30% of the population was obese or morbidly obese. Most subjects in the Phase 3 safety population were potentially able to bear children (80%) and 5% were post-menopausal. The most common methods of contraception reported were barrier methods (32%) and abstinence (19%), though data on contraception were missing for 20% of subjects. Approximately 7% of subjects had a diagnosis of diabetes mellitus.

Table 8-27 Other Baseline Characteristics – Pooled Phase 3 Safety Population

	Oral ibrexafungerp 300mg BID (N=545) n (%)	Placebo BID (N=275) n (%)	Total (N=820) n (%)
Body mass index (kg/m^2)			
Mean (SD)	27.9 (8.4)	28.5 (8.3)	28.1 (8.3)
Median (Min, Max)	25.7 (15.4, 65.9)	26.2 (17.2, 56.9)	25.8 (15.4, 65.9)
Body mass index group			
Normal (18.5 - <25 kg/m^2)	223 (40.9)	111 (40.4)	334 (40.7)
Obese (30 - < 40 kg/m^2)	133 (24.4)	60 (21.8)	193 (23.5)
Overweight (25 - < 30 kg/m^2)	114 (20.9)	59 (21.5)	173 (21.1)
Morbidly obese ($\geq$40 kg/m^2)	47 (8.6)	34 (12.4)	81 (9.9)
Underweight (<18.5 kg/m^2)	28 (5.1)	11 (4.0)	39 (4.8)
Fertility status			
Potentially Able to Bear Children	444 (81.5)	208 (75.6)	652 (79.5)
Surgically Sterile/Infertile	79 (14.5)	46 (16.7)	125 (15.2)
Post-Menopausal	22 (4.0)	21 (7.6)	43 (5.2)
Contraception method			
Barrier Methods Only	176 (32.3)	89 (32.4)	265 (32.3)
Abstinence	112 (20.6)	46 (16.7)	158 (19.3)
Oral Contraceptives	72 (13.2)	34 (12.4)	106 (12.9)
IUD	46 (8.4)	21 (7.6)	67 (8.2)
Depo Contraceptives (Implants/Injectables)	19 (3.5)	10 (3.6)	29 (3.5)
Vasectomized Partner	11 (2.0)	3 (1.1)	14 (1.7)
Other	4 (0.7)	4 (1.5)	8 (1.0)
Vaginal Ring	4 (0.7)	1 (0.4)	5 (0.6)
Missing Data	101 (18.5)	67 (24.4)	168 (20.5)
Diabetes mellitus diagnosis			
N	504 (92.5)	255 (92.7)	759 (92.6)
Y	41 (7.5)	20 (7.3)	61 (7.4)

Source: Clinical reviewer, OCS Demographics Tool v3 and OCS Analysis Studio version 1.4.2

Adequacy of the safety database:

The safety database is adequate to support the use of oral ibrexafungerp 300 mg BID for one-day for treatment of postmenarchal girls and women with acute VVC. The safety database included 575 women treated with the proposed VVC treatment dose and an additional 491 healthy men and women exposed to other oral ibrexafungerp doses and durations. The

demographics of the subjects in the Phase 3 trials were generally representative of the target population with VVC in the U.S. The trials contained fewer women with diabetes than in the expected target population (likely due to the exclusion criterion for poorly controlled diabetes), but the ibrexafungerp safety profile should be similar in patients with poorly controlled diabetes, particularly given the short duration of therapy for acute VVC. While the trials enrolled primarily healthy young and middle-aged women, the safety findings can be used to support the use of ibrexafungerp for treatment of VVC in postmenarchal adolescent girls and in older women.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

In the NDA submission, the Applicant noted some similar adverse events were split into multiple terms when coded to Medical Dictionary for Regulatory Activities (MedDRA) terminology. In the Adverse Reaction section of the proposed labeling, the Applicant combined multiple MedDRA preferred terms under the term "abdominal pain" (abdominal pain, abdominal pain upper, and abdominal pain lower) to address this issue but did not change the coding in the ADAE datasets.

On reviewing the ADAE datasets, the clinical reviewer identified additional adverse events that required recoding into more inclusive terms. Table 8-28 summarizes the number of events observed in the pooled Phase 3 safety population for each of the reviewer's recoded terms. The same events were also recoded in the datasets for the pooled Phase 1 safety population and the Phase 2 trials. The reviewer's proposed changes to the Adverse Reaction table of the label using these recoded terms are summarized in Section 13.1 *Prescription Drug Labeling*.

Table 8-28 Adverse Event Recoded Preferred Terms – Pooled Phase 3 Trials

Term used for reviewer recoding	Original Preferred Term	Oral ibrexafungerp 300mg BID No. of events	Placebo BID No. of events	Total No. of events
Abdominal pain		**68**	**15**	**83**
	Abdominal pain	28	5	33
	Abdominal pain upper	18	7	25
	Abdominal discomfort	19	2	21
	Abdominal pain lower	3	1	4
Dizziness		**18**	**7**	**25**
	Dizziness	18	6	24
	Dizziness postural	0	1	1
Fatigue		**15**	**7**	**22**
	Fatigue	15	6	21
	Asthenia	0	1	1

Hepatic enzyme increased[1]		**3**	**1**	**4**
	Alanine aminotransferase increased	2	1	3
	Hepatic enzyme increased	1	0	1
	Liver function test abnormal	1	0	1

[1]The preferred term "aspartate aminotransferase increased" was also recoded to "hepatic enzyme increased" in the ISS dataset, but this term was not reported in the Phase 3 pooled safety data
Source: Clinical reviewer, JMP v15.0

Categorization of Adverse Events

Adverse events (AEs) were defined as any untoward occurrence associated with the use of a drug, whether or not considered drug related. Laboratory abnormalities considered clinically significant by study investigators were reported as AEs. All AEs were followed to resolution, an outcome was reached, stabilization occurred, or the event was otherwise explained.

Treatment-emergent AEs (TEAEs) were defined as AEs that started or worsened after the first administration of study treatment and occurred up to 30 days after the last day of study treatment. For studies with a cross-over design, a TEAE occurring during a given treatment period was attributed to the treatment administered during that treatment period.

For the Phase 3 trials, AEs were reviewed at all scheduled and unscheduled visits and were recorded from the time informed consent was obtained through the Day 25±4 FU visit. Subjects used study diaries from Day 1 through the TOC visit to record daily vulvovaginal symptoms, other medical concerns or complaints, and concomitant medications. The investigators determined if any signs/symptoms or other medical concerns noted in the diaries should be reported as AEs.

Investigators graded AE severity on a protocol-defined scale using the following criteria:

- **Mild:** awareness of sign or symptom, but easily tolerated; not likely to require medical attention
- **Moderate:** discomfort enough to cause some interference with daily activity; may require medical intervention
- **Severe:** intense enough to disrupt daily activities; likely requires medical intervention

Investigators assessed causality based on the following classification:

- **Related:** The temporal relationship of the AE with the study drug makes causality possible and as likely or more likely than due to another cause such as other drugs, a surgical intervention, or an underlying disease
- **Not related:** The temporal relationship of the AE with the study drug makes causality improbable and can be due to another cause such as other drugs, a surgical intervention, or an underlying disease

In the Phase 3 protocols, the following events were defined as events of clinical interest (ECIs) and were required to be reported at the time of occurrence:

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 8 x the upper limit of normal (ULN), confirmed by repeat testing
- ALT or AST > 5 x ULN for more than 2 weeks if new compared to baseline, confirmed by repeat testing
- ALT or AST > 3 x ULN **and** total bilirubin >2 x ULN if new compared to baseline, confirmed by repeat testing
- ALT or AST > 3 x ULN, confirmed by repeat test, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)

For the Phase 3 trials, all AEs were coded using MedDRA version 21.1. For the Phase 1 safety data included in the ISS, AEs were recoded using MedDRA 21.1. For the Phase 2 studies, SCY-078-203 was coded using MedDRA version 18.1 and SCY-078-204 was coded using MedDRA version 20.1.

- ***Reviewer comments:*** *While the Phase 3 trials had an events of clinical interest definition for transaminase elevations, measurement of liver safety laboratory tests was only scheduled at a single timepoint 10 days after study treatment was completed.*

Routine Clinical Tests

For the Phase 3 trials, clinical safety laboratory testing was performed at screening, at the TOC visit at Day 11±3, and at unscheduled visits if needed. All tests were performed by a qualified central laboratory. Hematology testing consisted of complete blood counts with a differential white blood cell count. Serum chemistry testing consisted of sodium, potassium, creatinine, glucose, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), bilirubin (total, direct, and indirect), and total creatinine phosphokinase (CPK). Any subjects who experienced persistence, worsening, or recurrence of vaginitis symptom had vulvovaginal samples taken for KOH testing, pH measurements, investigation of other pathogens such as bacterial vaginosis and *T. vaginalis* (local laboratory), and fungal culture (central laboratory).

The following additional clinical tests were performed in a subset of Phase 1 trials to evaluate safety concerns identified during ibrexafungerp development:

- Assessment of effects on gastric mucosa
    - Serum gastrin concentration (SCY-078-001, SCY-078-002, SCY-078-008)
    - Upper endoscopy with gastric biopsies (SCY-078-002)
- Assessment of thrombotic effects (SCY-078-111)
    - Coagulation: pro-thrombin time (PT) and activated partial thromboplastin time (aPTT) at baseline and on Day 1 (post-AM dose), Day 3 (pre-AM dose), Day 5 (pre-AM dose), Day 7 (post-AM dose) of each dosing period
    - Thrombosis biomarkers: D-dimer and thrombin-antithrombin complex (TAT) at

baseline and on Day 1 (post-AM dose), Days 2-6 (pre-AM dose), Day 11 (96 h after last dose) of each dosing period

- Deep-vein thrombosis assessment: lower extremity ultrasound at baseline and Day 7 (2 h after last dose) of each dosing period

8.2.4. Safety Results

Deaths

There were no deaths in the safety database submitted to support oral ibrexafungerp 300 mg BID x 1 day for acute VVC.

The safety update from the ongoing clinical trials evaluating higher doses of oral ibrexafungerp for invasive fungal diseases reported 5 deaths (DSUR 05, IND 107521 SDN 0166). There were 2 deaths in Study SCY-078-301 (evaluating treatment of with fungal diseases refractory or intolerant of standard antifungal treatment), 2 deaths in Study SCY-078-305 (evaluating treatment of *C. auris*), and 1 death in Study SCY-078-206 (evaluating combination therapy with voriconazole for treatment of invasive pulmonary aspergillosis). Based on review of the event narratives, the clinical reviewer concluded the deaths were attributable to co-morbid medical conditions and unlikely to be related to oral ibrexafungerp.

The clinical study report from the Phase 2 pilot study of oral ibrexafungerp 500-750 mg daily for step-down therapy of invasive candidiasis reported 1 death in an ibrexafungerp-treated subject (SCY-078-202). Based on the review of the event narrative, the clinical reviewer concluded that the death was due to the subject's underlying illness.

- ***Reviewer comment:*** *There were no deaths related to oral ibrexafungerp treatment.*

Serious Adverse Events

In the pooled Phase 3 safety population, 2 ibrexafungerp-treated subjects (0.4%) experienced serious adverse events (SAEs, Table 8-29). Neither of these events were related to ibrexafungerp treatment in the clinical reviewer's opinion:

- A 47 y African American female (b) (6) with a history of aortic valve replacement and congestive heart failure was hospitalized with pneumonia and bronchial hypersensitivity on Day 9, discharged on Day 15 and completed the study.

- A 49 y White female (b) (6) developed a bacterial gastrointestinal infection on Day 11 that required treatment with IV antibacterial drugs; she recovered on Day 23 and completed the study.

Table 8-29 Serious Adverse Events – Pooled Phase 3 Trials

	Oral ibrexafungerp 300mg BID (N=545) n (%)	Placebo BID (N=275) n (%)	Total (N=820) n (%)
Any SAE	2 (0.4)	3 (1.1)	5 (0.6)
System Organ Class **Preferred Term**			
Infections and infestations			
Gastrointestinal bacterial infection	1 (0.2)	0	1 (0.1)
Pneumonia	1 (0.2)	0	1 (0.1)
Metabolism and nutrition disorders			
Diabetes mellitus	0	1 (0.4)	1 (0.1)
Diabetic ketoacidosis	0	1 (0.4)	1 (0.1)
Hypokalaemia	0	1 (0.4)	1 (0.1)
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity	1 (0.2)	0	1 (0.1)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

In the Phase 2 trials, there were no SAEs.

In the Phase 1 trials, 3 ibrexafungerp-treated subjects experienced SAEs (**Table 16-35**, Appendix). One SAE was not treatment-related: the discovery of a metastatic carcinoid tumor during a single dose ibrexafungerp study. Two SAEs were related to ibrexafungerp in the clinical reviewer's assessment:

- **Hypersensitivity reaction:** A 19 yo White male (b) (6) experienced a severe hypersensitivity reaction following oral ibrexafungerp 750 mg BID for 2 days. He developed myalgias and presyncope after 2 doses, then worsening myalgias and a tender rash on his hands after 2 additional doses. Study treatment was discontinued. Over the next day, he experienced fever (37.7°C), severe myalgias/arthralgias, postural hypotension, lethargy, and worsening blistering rash without mucosal involvement. Laboratory testing showed increased WBC count with neutrophilia and elevated C-reactive protein, but normal liver function, kidney function, and creatinine kinase. The subject was hospitalized and improved with steroid therapy. The Investigator suspected acute drug-induced febrile neutropenia (Sweet's syndrome) but given the lack of biopsy data, the term "Type 4 hypersensitivity reaction" was reported.

- **Hepatic enzymes increased:** A 27 yo African American male (b) (6) experienced severe transaminitis following a single dose of oral ibrexafungerp 500 mg. He reported mild crampy abdominal pain and scheduled laboratory testing 24 hours post-dosing demonstrated ALT 404 U/L and AST 513 U/L, with alkaline phosphatase and

total bilirubin within normal limits. Serological testing for viral hepatitis was negative. Ultrasound showed mild intra-ductal dilation. Magnetic resonance cholangial-pancreatography (MRCP) was normal. Transaminases normalized within 2 weeks. The subject was evaluated by a hepatologist and an idiosyncratic drug reaction was suspected.

The 120-Day Safety Update reported 2 subjects experiencing SAEs from the ongoing blinded, placebo-controlled Phase 3 trial evaluating oral ibrexafungerp 300 mg BID x 1 day repeated monthly for prevention of recurrent VVC. One subject was hospitalized due to complications of SARS-CoV-2 infection and one subject was hospitalized due a hemorrhagic ovarian cyst during the fluconazole lead-in phase. Neither event was related to study treatment in the clinical reviewer's opinion.

- ***Reviewer comments:*** *There were no SAEs related oral ibrexafungerp in the Phase 2 or 3 trials evaluating treatment of VVC.*

  There were 2 SAEs related to oral ibrexafungerp in Phase 1 trials: hypersensitivity reaction (750 mg BID x 2 days) and increased hepatic enzymes (500 mg x 1 dose). These reactions may also occur with use of the oral ibrexafungerp dosing proposed for acute VVC treatment (300 mg BID x 1 day).

Dropouts and/or Discontinuations Due to Adverse Effects

In the pooled Phase 3 safety population, the most common reason for study discontinuation was lack of efficacy and/or use of antifungal therapy prior to the TOC visit (Table 8-30). These discontinuations were more frequent in the placebo arm (29%) than the ibrexafungerp arm (16%). All discontinuations due to TEAEs occurred in the ibrexafungerp arm (8 subjects, 1.5%). Of these, 2 subjects experienced TEAEs that were likely related to study treatment: vomiting and dizziness. The other 6 TEAEs were unrelated (bacterial vaginosis in 4 subjects, worsening diabetes in 1 subject, vulvovaginal pruritus in 1 subject). All discontinuations due to study withdrawals by subjects occurred in the ibrexafungerp arm (5 subjects, 0.9%); one of these subjects had a reported TEAE (gastroenteritis, mild, Day 1).

Table 8-30 Study Discontinuations – Pooled Phase 3 Trials

	Oral ibrexafungerp 300mg BID (N=545) n (%)	Placebo BID (N=275) n (%)	Total (N=820) n (%)
Study discontinued	116 (21.3)	93 (33.8)	209 (25.5)
Reason for study discontinuation			
Lack of efficacy and/or use of antifungal therapy prior to TOC	88 (16.1)	80 (29.1)	168 (20.5)
Adverse event [1]	8 (1.5)	0 (0.0)	7 (0.9)
Lost to follow-up	5 (0.9)	2 (0.7)	7 (0.9)

Use of antifungal therapy after TOC (but prior to FU visit) [1,2]	5 (0.9)	2 (0.7)	7 (0.9)
Withdrawal by subject	6 (1.1)	0 (0.0)	5 (0.6)
Sponsor decision [3]	2 (0.4)	2 (0.7)	4 (0.5)
Pregnancy	2 (0.4)	0 (0.0)	2 (0.2)
Protocol violation (ineligible subject)[4]	1 (0.2)	4 (1.5)	5 (0.6)
Other[5]	1 (0.2)	1 (0.4)	2 (0.2)
Physician decision	0 (0.0)	2 (0.7)	2 (0.2)

[1] One subject reclassified by the clinical reviewer from "Lack of Efficacy and/or Use of Antifungal prior to TOC" to "Adverse Event" due to an AE resulting in study discontinuation (vulvovaginal pruritus) in the ADAE dataset.
[2] One subject reclassified by the clinical reviewer from the "Withdrawal by Subject" category to the "Use of Antifungal" category due to the comment field reporting the subject was withdrawn for use of fluconazole prior to the end of study visit.
[3] Four subjects were reclassified by the clinical reviewer from the "Other" category to "Sponsor Decision" based on the comment field in the ISS dataset. Three of these subjects were discontinued by the Sponsor due to evidence of poorly controlled diabetes post-randomization.
[4] Five subjects were reclassified by the clinical reviewer from the "Other" category to "Protocol Violation" based on the comment field in the ISS dataset. Reasons for ineligibility were: did not have minimum VVS score $\geq$4 with at least 2 signs or symptoms with score $\geq$2 (3 subjects, placebo arm), did not have vaginal pH $\leq$4.5 (1 subject, placebo arm), vaginal condition other than acute VVC that may interfere with evaluation (1 subject, ibrexafungerp arm).
[5] "Other" reasons for study discontinuation were HSV positive (placebo arm) and subject unable to return for TOC visit (ibrexafungerp arm)
Source: Clinical reviewer, JMP v15

In the Phase 2 trials, there were no study discontinuations due to TEAEs among the 64 ibrexafungerp-treated subjects in the SCY-078-203 proof-of-concept trial evaluating 3-5 doses of oral ibrexafungerp for moderate to severe recurrent VVC. In the SCY-078-204 dose-finding trial, 2/153 ibrexafungerp-treated subjects (1.3%) discontinued the study due to TEAEs (gastrointestinal TEAEs in both subjects and dizziness in one of the subjects). Both received oral ibrexafungerp 750 mg as a single dose (Table 16-37, Appendix).

In the pooled Phase 1 safety population, 8/298 ibrexafungerp-treated subjects (2.7%) discontinued the study due to adverse events (Table 16-37, Appendix). Three of these events were SAEs discussed in the previous section (metastatic carcinoid tumor, type IV hypersensitivity, and increased hepatic enzymes). One additional subject (oral ibrexafungerp 500 mg single dose) also developed increased hepatic enzymes resulting in study discontinuation. The other TEAEs resulting in study discontinuation were malaise and gastrointestinal disorders (nausea, vomiting, diarrhea, abdominal pain).

- ***Reviewer comments:*** *In the Phase 3 trials, the most common reason for study discontinuation was lack of efficacy, though these discontinuations occurred more frequently in the placebo arm than the ibrexafungerp arm. All discontinuations due to adverse events occurred in the ibrexafungerp arm, but few were related to ibrexafungerp treatment in the reviewer's opinion.*

In the Phase 1 trials, 2 healthy volunteers discontinued the study due to increased hepatic enzymes and one of these was a serious adverse event.

Significant Adverse Events

In the pooled Phase 3 safety population, more subjects experienced TEAEs in the ibrexafungerp arm (46%) than the placebo arm (39%, Table 8-31). All of the subjects experiencing TEAEs leading to study treatment withdrawal (2 subjects, 0.4%) or interruption (2 subjects, 0.4%) were in the ibrexafungerp arm. Of the 5 subjects (0.9%) experiencing severe TEAEs in the ibrexafungerp arm, one event was related to study treatment in the reviewer's opinion: severe nausea with onset on Day 1. The other 4 ibrexafungerp-treated subjects experienced severe TEAEs that were unlikely to be related to study treatment: genital herpes, pneumonia/bronchial hyperreactivity, nausea (onset Day 6), diabetes mellitus.

Table 8-31 Overview of Treatment-Emergent Adverse Events – Pooled Phase 3 Trials

	Oral ibrexafungerp 300mg BID (N=545)	Placebo BID (N=275)	Total (N=820)
Any TEAE	249 (45.7)	107 (38.9)	356 (43.4)
SAE	2 (0.4)	3 (1.1)	5 (0.6)
TEAEs leading to change in study treatment			
Drug interrupted	2 (0.4)	0	2 (0.2)
Drug withdrawn	2 (0.4)	0	2 (0.2)
TEAEs leading to study discontinuation	8 (1.5)	0	8 (1.0)
TEAE severity			
Mild	218 (40.0)	84 (30.5)	302 (36.8)
Moderate	67 (12.3)	35 (12.7)	102 (12.4)
Severe	5 (0.9)	8 (2.9)	13 (1.6)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

In the Phase 2 trials, the TEAE incidence was higher in cohorts with larger total daily doses of ibrexafungerp (Table 16-38, Appendix).

- In the SCY-078-203 proof-of-concept trial, the TEAE incidence in the ibrexafungerp arms (1250 mg loading dose followed by 750 mg daily for a total of 3-5 doses) was approximately 90%. In contrast, the fluconazole comparator arm had a TEAE incidence of 12.5%. However, there were no severe TEAEs or TEAEs resulting in treatment discontinuation in the trial.

- In the SCY-078-204 dose-ranging trial, the TEAE incidence was 70-80% in the cohorts receiving the highest total daily doses of ibrexafungerp (750-900 mg for 1 day) compared to 55-60% in the cohorts with lower doses (300-600 mg for 1-3 days). Two subjects (6.2%) in the cohort receiving 750 mg oral ibrexafungerp discontinued the study due to TEAEs (gastrointestinal events and dizziness, previously discussed in Adverse Drop-outs section). Across the ibrexafungerp study cohorts in the SCY-078-204 trial, 8 subjects (4.3%) experienced severe TEAEs. Six of these severe TEAEs were possibly related to ibrexafungerp: elevated CPK on Day 6, headache on Day 1, and gastrointestinal symptoms (vomiting, diarrhea, abdominal pain) on Day 1.

- In the SCY-078-204 cohort receiving the proposed acute VVC oral ibrexafungerp dose of 300 mg BID for 1 day, only one subject (3.3%) experienced a severe TEAE: muscle spasms on Day 9 (unrelated to study treatment in the reviewer's assessment).

In the pooled Phase 1 safety population, approximately 50% of subjects receiving single doses and 75% of subjects receiving multiple doses of oral ibrexafungerp experienced TEAEs (Table 16-39, Appendix). Five subjects (1.7%) had drug withdrawn due to TEAEs. Four subjects (1.3%) experienced severe TEAEs; three of these were also classified as SAEs and were discussed in the previous section. The fourth subject experienced severe abdominal pain following a single oral dose of ibrexafungerp 1600 mg; this event was likely related to ibrexafungerp treatment.

The Applicant's statistical analysis plan for the integrated summary of safety contained post-hoc definitions for the following adverse events of special interest (AESI) in the Phase 2 dose-finding trial (SCY-078-204) and the Phase 3 trials (VANISH-303 and VANISH-306):

- **Drug-related hepatic disorders:** This AESI definition included a list of terms for liver diseases and signs/symptoms of severe hepatic dysfunction. The list corresponded to the narrow Standardized MedDRA Query (SMQ) "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ [20000013]," a subset of "Drug related hepatic disorders – severe events only SMQ [20000007]." Common clinical signs of liver injury such as jaundice or abnormal liver enzymes were not included in the AESI definition. There were no events in the Phase 2 dose-finding trial or the Phase 3 trials meeting this definition.

- **Gastrointestinal disorders:** This AESI definition included a list of terms for signs/symptoms of gastrointestinal distress such abdominal pain, bloating, diarrhea, and nausea. In the Phase 2 dose-finding trial, 36.7% (11/30) subjects receiving 1 day of oral ibrexafungerp 300 BID experienced TEAEs meeting this definition, while the incidence rose to 62.5% (20/32) in the cohort receiving a 750 mg single dose of ibrexafungerp. In the Phase 3 VVC treatment trials, the incidence of events identified with this definition was 31.6% (172/545) in the ibrexafungerp-treated subjects and 14.2% (39/275) in placebo-treated subjects.

- **Torsade de pointes/QT prolongation:** This AESI definition corresponded to the SMQ "Torsade de pointes/QT prolongation SMQ [20000001]" plus the addition of the event term "seizure." There were no events in the Phase 2 dose-finding trial or the Phase 3 trials meeting this definition.

- ***Reviewer comments:*** *While ibrexafungerp-treated subjects experienced more TEAEs than placebo-treated subjects in Phase 3 trials, most events were mild or moderate. The TEAE incidence increased with increasing dose and/or duration of oral ibrexafungerp treatment in the Phase 2 trials.*

  Among subjects receiving the proposed oral ibrexafungerp VVC treatment of 300 mg BID x 1 day, one-third experienced gastrointestinal adverse events meeting the Applicant's AESI definition.

Treatment Emergent Adverse Events and Adverse Reactions

For the pooled Phase 3 safety population, the most common TEAEs (≥2% of subjects) are summarized in Table 8-32. Gastrointestinal events were most frequently associated with oral ibrexafungerp treatment, with > 10% of ibrexafungerp-treated subjects experiencing diarrhea, nausea, and/or abdominal pain. Two other TEAEs were less common but occurred at higher frequencies in the ibrexafungerp-treated subjects: dizziness (3.3% ibrexafungerp, 2.5% placebo) and vomiting (2.0% ibrexafungerp, 0.7% placebo). Headache occurred in approximately 8% of subjects in the Phase 3 trials, but the incidence was similar in the treatment arms (8.3% ibrexafungerp, 8.0% placebo). Most TEAEs, including gastrointestinal events, were mild and lasted ≤ 3 days (Table 16-40 and Table 16-41, Appendix).

Table 8-32 TEAE Occurring in ≥2% Subjects – Pooled Phase 3 Trials

System Organ Class Preferred Term	**Oral ibrexafungerp 300mg BID (N=545) n (%)**	**Placebo BID (N=275) n (%)**	**Total (N=820) n (%)**
Gastrointestinal disorders			
Diarrhoea	91 (16.7)	9 (3.3)	100 (12.2)
Nausea	65 (11.9)	11 (4.0)	76 (9.3)
Abdominal pain[1]	62 (11.4)	14 (5.1)	76 (9.3)
Vomiting	11 (2.0)	2 (0.7)	13 (1.6)
General disorders and administration site conditions			
Fatigue[2]	15 (2.8)	7 (2.5)	22 (2.7)
Infections and infestations			
Bacterial vaginosis	17 (3.1)	12 (4.4)	29 (3.5)
Nervous system disorders			

System Organ Class Preferred Term	Oral ibrexafungerp 300mg BID (N=545) n (%)	Placebo BID (N=275) n (%)	Total (N=820) n (%)
Headache	45 (8.3)	22 (8.0)	67 (8.2)
Dizziness[3]	18 (3.3)	7 (2.5)	25 (3.0)

[1]Includes terms "abdominal pain," "abdominal pain upper," "abdominal pain lower," and "abdominal discomfort."
[2]Includes terms "fatigue" and "asthenia"
[3] Includes terms "dizziness" and "postural dizziness"
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

The clinical reviewer analyzed the TEAEs reported in < 2% of subjects in the Phase 3 trials to identify events likely to represent less common oral ibrexafungerp adverse reactions. Events were included in Table 8-33 if they occurred at a higher incidence (≥ 0.5%) in the ibrexafungerp arm than the placebo arm or if additional data from the Phase 1 or Phase 2 trials supported a relationship between the event and ibrexafungerp administration.

Table 8-33 Adverse Reactions Occurring in < 2% of Subjects -- Pooled Phase 3 Trials

System Organ Class Preferred Term	Oral ibrexafungerp 300mg BID (N=545) n (%)	Placebo BID (N=275) n (%)	Clinical reviewer comments	Recommendations
Reproductive system and breast disorders Dysmenorrhoea	7 (1.3)	2 (0.7)	Incidence 0.6% higher in ibrexafungerp arm; it is possible that abdominal pain due to ibrexafungerp was attributed to menstrual pain	Add term to labeling
Gastrointestinal disorders Flatulence	6 (1.1)	1 (0.4)	Incidence 0.7% higher in ibrexafungerp arm; consistent with other gastrointestinal symptoms attributable to ibrexafungerp	Add term to labeling
Musculoskeletal and connective tissue disorders Back pain	6 (1.1)	1 (0.4)	Incidence 0.7% higher in ibrexafungerp arm; could be related to the abdominal pain or other gastrointestinal symptoms attributable to ibrexafungerp	Add term to labeling
Infections and infestations Gastroenteritis	5 (0.9)	1 (0.4)	Incidence 0.5% higher in ibrexafungerp arm; however likely the same symptoms (nausea, vomiting, diarrhea) reported in common adverse reaction table and not due to infectious gastroenteritis	Do not add term to labeling

Investigations Hepatic enzyme increased	4 (0.7)	1 (0.4)	Incidence slightly higher (0.3%) in the ibrexafungerp arm, but given additional reports in Phase 1 and 2 trials likely represents an adverse reaction	Add modified term to labeling: elevated transaminases
Reproductive system and breast disorders Vaginal haemorrhage	3 (0.6)	0 (0.0)	Incidence 0.6% higher in ibrexafungerp arm; verbatim terms were vaginal spotting and abnormal vaginal bleeding; it is unclear why there were 3 events in ibrexafungerp arm and none in placebo. There was an additional ibrexafungerp-treated subject in Phase 2 (SCY-078-204) with a TEAE of moderate vaginal bleeding; therefore will include as a possible adverse reaction	Add modified term to labeling: vaginal bleeding
Skin and subcutaneous tissue disorders Rash	2 (0.4)	2 (0.7)	Incidence is not higher in the ibrexafungerp arm but given additional hypersensitivity reports from Phase 1 trials (including hypersensitivity reaction SAE with skin rash in the Phase 1 oral ibrexafungerp trial SCY-078-108) this may represent an adverse reaction	Add modified term to labeling: rash/hypersensitivity reaction

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

In the Phase 3 trials, the overall TEAE incidence was higher in the U.S. (56% of subjects reporting TEAEs) compared to Bulgaria (20%, Table 8-34). The incidence of TEAEs in the ibrexafungerp arm was similar to the placebo arm in Bulgaria, while there was a higher TEAE incidence in the ibrexafungerp arm (60%) than in the placebo arm (47%) in the U.S. However, the most common TEAEs in the ibrexafungerp arm at the U.S. sites (diarrhea, nausea, abdominal pain) were also the most common TEAEs at the Bulgarian sites. Headache was also a common TEAE in the Bulgarian sites, but as in the U.S. sites, headache occurred at similar rates in the ibrexafungerp arm (4.7%) and placebo arm (5.9%).

Table 8-34 TEAE Incidence by Country – Pooled Phase 3

	Oral ibrexafungerp 300mg BID		**Placebo BID**		**Total**	
	USA (N=352) n(%)	**Bulgaria (N=193) n(%)**	**USA (N=190) n(%)**	**Bulgaria (N=85) n(%)**	**USA (N=542) n(%)**	**Bulgaria (N=278) n(%)**
Any TEAE	212 (60.2)	37 (19.2)	89 (46.8)	18 (21.2)	301 (55.5)	55 (19.8)
Any SAE	1 (0.3)	1 (0.5)	3 (1.6)	0	4 (0.7)	1 (0.4)
TEAE severity						

	Oral ibrexafungerp 300mg BID		Placebo BID		Total	
	USA (N=352) n(%)	Bulgaria (N=193) n(%)	USA (N=190) n(%)	Bulgaria (N=85) n(%)	USA (N=542) n(%)	Bulgaria (N=278) n(%)
Mild	183 (52.0)	35 (18.1)	68 (35.8)	16 (18.8)	251 (46.3)	51 (18.3)
Moderate	63 (17.9)	4 (2.1)	31 (16.3)	4 (4.7)	94 (17.3)	8 (2.9)
Severe	5 (1.4)	0	8 (4.2)	0	13 (2.4)	0
TEAEs ≥2% incidence by SOC and PT						
Gastrointestinal disorders						
Diarrhoea	84 (23.9)	7 (3.6)	9 (4.7)	0	93 (17.2)	7 (2.5)
Nausea	59 (16.8)	6 (3.1)	11 (5.8)	0	70 (12.9)	6 (2.2)
Abdominal pain	52 (14.8)	10 (5.2)	13 (6.8)	1 (1.2)	65 (12.0)	11 (4.0)
Vomiting	8 (2.3)	3 (1.6)	1 (0.5)	1 (1.2)	9 (1.7)	4 (1.4)
General disorders and administration site conditions						
Fatigue	14 (4.0)	1 (0.5)	7 (3.7)	0	21 (3.9)	1 (0.4)
Infections and infestations						
Bacterial vaginosis	16 (4.5)	1 (0.5)	12 (6.3)	0	28 (5.2)	1 (0.4)
Nervous system disorders						
Headache	36 (10.2)	9 (4.7)	17 (8.9)	5 (5.9)	53 (9.8)	14 (5.0)
Dizziness	17 (4.8)	1 (0.5)	6 (3.2)	1 (1.2)	23 (4.2)	2 (0.7)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

In the Phase 2 trials, the TEAEs reported following oral ibrexafungerp administration were similar to the Phase 3 trials (Table 16-42 and Table 16-43, Appendix):

- Diarrhea, nausea and abdominal pain were the most common TEAEs. Diarrhea occurred frequently in subjects receiving the highest doses of ibrexafungerp, with incidence of 60-80% in the SCY-078-203 cohorts receiving a 1250 mg loading dose of ibrexafungerp followed by 750 mg daily for 3-5 days total.

- Headache was reported in more subjects receiving the 5-day ibrexafungerp course (4/32, 12.5%) than the 3-day course (1/32, 3.1%) or fluconazole (1/32, 3.1%) in the SCY-078-203 trial. In the SCY-078-204 dose-ranging trial, headache was reported in 22/153 ibrexafungerp-treated subjects (14.4%), but the incidence was not dose-related and 2/32 fluconazole-treated subjects (6.2%) also reported headache.

- Elevated CPK was reported as a TEAE in 5/153 ibrexafungerp-treated subjects (3.3%) in SCY-078-204. However, CPK elevations were more common at lower doses of ibrexafungerp and 1 event was also reported in the fluconazole control arm. According to the clinical study report, non-drug causes (exercise, recent injections) were associated with some of the elevated CPK events.

In the pooled Phase 1 safety population, diarrhea, abdominal pain, and/or nausea occurred in ≥20% of subjects, with the highest incidence in cohorts receiving multiple ibrexafungerp doses (Table 16-44, Appendix). Vomiting and dizziness, the two other events occurring more frequently in the ibrexafungerp arms of the Phase 3 safety population, were also common in the Phase 1 population and were seen at higher frequency in the cohorts receiving multiple ibrexafungerp doses. Headache was reported by 10-20% of subjects in the Phase 1 trials.

One Phase 1 trial (SCY-078-102) evaluated a single dose of 500 mg oral ibrexafungerp citrate in the fed (following a high-fat meal) and fasted state. Based on the data from this study, the Applicant stated (b) (4) that the frequency of nausea may be reduced when oral ibrexafungerp is taken with food. The overall incidence of gastrointestinal adverse events was similar when a single dose of oral ibrexafungerp was administered in the fed (9/24, 38%) or fasted state (7/22, 32%, Table 8-35). While nausea was observed more frequently in the fasted state (4/22, 17%) than the fed state (0/22), the number of subjects evaluated is not large enough to draw definitive conclusions about the effect of food on the incidence of adverse reactions.

Table 8-35 Gastrointestinal TEAEs in the Fed and Fasted State – Phase 1 Trial SCY-078-102

	Oral ibrexafungerp 500mg citrate tables Fasted state (N=24) n(%)	**Oral ibrexafungerp 500mg citrate tables Fed state (N=22) n(%)**
Any TEAE in Gastrointestinal Disorders SOC	9 (37.5)	7 (31.8)
Diarrhoea	6 (25.0)	5 (22.7)
Nausea	4 (16.7)	0
Abdominal pain	3 (12.5)	4 (18.1)
Anorectal discomfort	1 (4.2)	0
Dyspepsia	1 (4.2)	0

Source: Clinical reviewer, OCS Analysis Studio, version 1.4.2

In response to an Information Request, the Applicant provided summary safety data from a recently completed PK study in adolescents [SCY-078-120, *A Phase 1, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Oral Ibrexafungerp (SCY-078) in Adolescent Female Subjects*]. The study was conducted in Mauritius and enrolled 10 subjects

with vaginitis that in the opinion of the Investigator was caused by *Candida* sp. infection and could benefit from antifungal treatment. All subjects received oral ibrexafungerp 300 mg BID for 1 day. Four subjects were enrolled in Cohort A (12-14 y); none experienced TEAEs. Six subjects were enrolled in Cohort B (15-17 y). Two of these subjects experienced mild TEAEs: vomiting in one subject and vomiting and abdominal pain in one subject.

- ***Reviewer comments:*** *The most common oral ibrexafungerp adverse reactions in the pooled Phase 3 safety population were gastrointestinal disorders: diarrhea (17%), nausea (12%), abdominal pain (11%), vomiting (2%). There are not enough data to conclude that taking oral ibrexafungerp with food has a mitigating effect on nausea.*

  Dizziness also appeared to be associated with ibrexafungerp treatment, with an increased incidence in ibrexafungerp-treated subjects (3.3%) compared to placebo-treated subjects (2.5%) in the Phase 3 trials. Two ibrexafungerp-treated subjects in the safety database had study discontinuations due to dizziness (one in Phase 2 and one in Phase 3).

  While headache was reported frequently in the Phase 3 safety population, the incidence was similar in ibrexafungerp-treated subjects (8.3%) and placebo-treated subjects (8.0%).

  Summary safety data from a recently completed PK study in which 10 adolescents received oral ibrexafungerp 300 mg BID x 1 day showed similar gastrointestinal adverse reactions to those reported in the VVC treatment trials enrolling adults.

Laboratory Findings

In the Phase 3 trials, routine post-treatment laboratory safety testing was performed at the TOC visit (Day 11±3). Laboratory test results were not graded by severity. In the pooled Phase 3 ADLB dataset, the clinical reviewer used descriptive statistics to compare the baseline and post-baseline laboratory test results by treatment group and found no differences.

In the pooled Phase 3 ADAE dataset, the most common adverse event in the Investigations SOC was elevated creatinine phosphokinase (10 subjects), but the incidence was higher in the placebo-treated subjects (1.8%) than the ibrexafungerp-treated subjects (0.9%). In the Phase 1 pooled ADAE dataset, the most common TEAE in the Investigations SOC was “red blood cells urine positive,” reported in 4 subjects enrolled in the single center Phase 1 trial evaluating multiple ascending doses of oral ibrexafungerp phosphate tablets (300-800 mg x 10 days, SCY-078-002). The only other hematuria TEAEs in the safety database occurred in the Phase 3 trials, with 1 TEAE with the preferred term “haematuria” reported in each arm (though routine urinalyses were not performed in the Phase 3 trials).

The Phase 3 trials had pre-specified criteria for events of clinical interest (ECIs) related to transaminase elevations: $\geq$8x upper limit of normal (ULN) confirmed on repeat testing, $\geq$5x ULN

for more than 2 weeks, ≥3x ULN with total bilirubin >2x ULN, or ≥3x ULN with associated clinical findings (fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, eosinophilia). Although 2 subjects met these criteria in the Phase 1 trials, no ECIs were identified in the Phase 3 trials. There were 2 ibrexafungerp-treated subjects in the Phase 3 trials with transaminase elevations ≥ 3x ULN post-treatment, but both had similar transaminase elevations at baseline (Table 8-36). Across the oral ibrexafungerp safety database, 5 subjects had transaminases ≥ 3x ULN (Table 8-36). No subjects met the criteria for Hy's Law (AST or ALT ≥3x ULN with bilirubin ≥ 2x ULN).

The adverse event "hepatic enzymes increased" was reported in 12/1067 subjects (1.1%) in the oral ibrexafungerp safety database. In the Phase 3 trials, TEAEs for elevated hepatic enzymes (assessed on Day 11) occurred in 4/545 (0.7%) ibrexafungerp-treated subjects and 1/275 (0.4%) placebo-treated subjects. In the Phase 2 trials, no subjects had TEAEs for hepatic enzyme elevations in SCY-078-203 (assessed on Day 5) and 4/153 (2.6%) ibrexafungerp-treated subjects had TEAEs for hepatic enzyme elevations in SCY-078-204 (assessed on Day 10). In the Phase 1 trials, 4/289 (1.3%) of ibrexafungerp-treated subjects had TEAEs for hepatic enzyme elevations (assessed at various timepoints) and all of the events were reported in single-dose cohorts.

Table 8-36 Ibrexafungerp-treated Subjects with Transaminase Elevations ≥ 3x ULN – All Trials

	Subject ID	Oral ibrexafungerp dose	Test	Peak level (U/L)	Study Day	TEAE comments
Phase 1	(b) (6)	500 mg single dose	ALT	613	2	Day 2 abdominal pain, hepatic enzyme increased
			AST	596	2	
		500 mg single dose[1]	ALT	367	38	Day 1 nausea and headache; Day 11 nausea; Day 20 liver enzymes increased
			AST	164	38	
Phase 2		300 mg BID on Days 1 to 3	ALT	116	10	Day 3 diarrhea
Phase 3		300 mg BID on Day 1	ALT	163	10	Day 10 liver enzymes increased *(Note: screening ALT 151 U/L)*
			AST	133	28	
		300 mg BID on Day 1	ALT	103	11	Day 2 nausea, vomiting abdominal pain *(Note: screening ALT 111 U/L)*

[1]In trial SCY-078-102, subjects received 500 mg x1 oral dose of ibrexafungerp phosphate in Treatment Period 1 followed ≥ 10 d later by 500 mg x1 oral dose of ibrexafungerp citrate in Treatment Period 2 followed ≥ 10 d later by 500 mg x1 oral dose of ibrexafungerp citrate in the fed state in Treatment Period 3. The peak transaminases in subject SCY-078-102-101-109 were observed in Treatment Period 3.
Source: Clinical reviewer, JMP v15

Two of the Phase 1 trials had laboratory measurements added to assess specific safety concerns:

- **Serum gastrin:** Since degeneration of gastric mucosa and elevated plasma gastrin concentrations were observed in 28-day oral ibrexafungerp nonclinical studies of rats and dogs, early Phase 1 trials measured serum gastrin concentration in healthy volunteers administered oral ibrexafungerp at single doses up to 1600 mg and multiple doses up to 800 mg x 28 days (SCY-078-001, SCY-078-002, SCY-078-008). All serum gastrin levels from these studies were within normal range (<100-115 pg/mL depending on the laboratory reference range). Though not submitted in the ADLB dataset, the clinical study report for the oral ibrexafungerp-pantoprazole DDI study (SCY-078-015) also notes that gastrin was measured and there was no difference in mean concentrations when co-administered with this proton pump inhibitor.

- **Coagulation tests and thrombosis biomarkers:** Following the development of thrombotic events in healthy volunteers receiving 250-375 mg IV ibrexafungerp daily in a multiple ascending dose Phase 1 trial (SCY-078-109), coagulation tests and daily thrombosis biomarkers were added to the safety assessments of a Phase 1 randomized, double-blind, placebo-controlled, cross-over, multiple dose trial evaluating safety and PK of oral ibrexafungerp (750 mg BID x 2 days then 750 mg daily x 5d, SCY-078-111).
    - PT/INR and aPTT were unremarkable in all subjects.
    - Thrombin-antithrombin (TAT) complex measurement, which was performed by a laboratory-developed assay, did not provide usable data. All subjects had TAT results outside the reference range (>3.9 µg/mL) at baseline, during placebo treatment, and during active treatment at various times during the study.
    - Mean D-dimer concentration was higher following ibrexafungerp dosing than following placebo dosing. D-dimer concentrations increased above the normal range ($\geq$ 500 ng/mL) in 4/16 subjects (25%) following ibrexafungerp dosing; one additional subject also had an elevated D-dimer following both ibrexafungerp and placebo dosing (Table 8-37). The onset of the D-dimer abnormalities was Day 3-11 after initiation of ibrexafungerp dosing.

Table 8-37 Subjects With Post-Treatment D-dimer Elevations – SCY-078-111

Subject ID	Study Treatment	Study Day Post-treatment	D-dimer ng/mL
Elevated D-dimer after ibrexafungerp treatment only			
(b) (6)	Ibrexafungerp	11	572
		3	611
		4	534
		6	534
(b) (6)		4	531
		6	508
Elevated D-dimer after ibrexafungerp treatment and placebo treatment			
(b) (6)	Ibrexafungerp	6	610
		11	532

	Placebo	3	641
		4	538

Source: Clinical reviewer, JMP v 15

- ***Reviewer comments:*** *Two laboratory abnormalities are potentially associated with oral ibrexafungerp administration: elevated transaminases and elevated D-dimer.*

  Transaminase elevations were more common in the Phase 1 trials than in the Phase 3 trials, but laboratory testing in the Phase 3 trials was limited to single timepoint 10 days after ibrexafungerp dosing was complete. It is unclear if the difference is due to a lower incidence of transaminase elevation with the 1-day 300 mg BID treatment course or decreased detection of transient transaminase elevations with the timing of the single transaminase measurement in the Phase 3 trial. No Hy's law cases were seen. Given that the treatment duration for acute VVC is only 1 day, the clinical impact of undetected transient transaminitis is likely limited.

  Post-treatment D-dimer elevations were observed in the one oral ibrexafungerp trial where this biomarker was assessed. This trial evaluated a higher dose (750 mg BID loading dose then 750mg daily) and longer duration of ibrexafungerp dosing (1 week). The abnormal D-dimer results were observed at least 3 days after dosing was initiated; therefore, the impact of the 1-day 300 mg PO BID acute VVC treatment regimen is likely to be limited. The absence of the thrombotic TEAEs in the oral ibrexafungerp trials is reassuring, but measurement of D-dimer may need to be considered for trials assessing higher doses and/or longer durations to more fully evaluate this finding.

Vital Signs

For the Phase 3 trial safety dataset, the clinical reviewer used descriptive statistics to compare changes in vital sign parameters (temperature, blood pressure, heart rate, respiratory rate) between the baseline visit and the TOC/early withdrawal visit and found no substantial differences between treatment arms.

Review of TEAEs related to vital sign changes in the safety database identified the following:

- In the Phase 3 trials, the only vital sign-related TEAEs were increased blood pressure (1 subject each arm) and increased heart rate (1 subject each arm).

- In the Phase 2 trials, one subject in the SCY-078-203 trial (1250 mg then 750 mg daily ibrexafungerp 3-day cohort) experienced a TEAE of moderate tachycardia on Day 1 and one subject in the SCY-078-204 trial (150 mg BID ibrexafungerp 3-day cohort) experienced a TEAE of mild tachycardia on Day 2.

- In the Phase 1 pooled safety dataset, there was a cluster of subjects with orthostatic vital sign changes reported as TEAEs in a single center Phase 1 trial evaluating multiple

ascending doses of oral ibrexafungerp phosphate tablets (SCY-078-002). The events were spread across the dosing cohorts (300 mg, 600 mg, or 800 mg oral ibrexafungerp x 10 days). All events were asymptomatic and transient except for a single moderate severity presyncopal event in a subject receiving 800 mg oral ibrexafungerp. The presyncopal event occurred on the first day of dosing, the subject recovered within 4 minutes, and dosing was continued through Day 10 without a repeat occurrence.

- ***Reviewer comments:*** *There did not appear to be any association of oral ibrexafungerp with vital sign changes.*

Electrocardiograms (ECGs)

There were no ECG data collected in the Phase 2 or Phase 3 trials. In the Phase 1 pooled safety database, the clinical reviewer used descriptive statistics to compare changes in ECG parameters (PR interval, QRS duration, QT interval, ventricular rate) before and after treatment across study groups. No substantial differences were identified in these parameters following oral ibrexafungerp treatment.

QT

The Applicant submitted cardiac safety data obtained in the SCY-078-106 Phase 1 IV ibrexafungerp trial in lieu of a dedicated TQT study. SCY-078-106 was a double-blind, randomized, placebo-controlled single-ascending dose trial evaluating IV ibrexafungerp doses of 30-375 mg in 16 healthy volunteers. The trial also had a planned multiple-ascending dose phase, but the study was stopped due to local tolerability issues with repeat IV infusions.

The FDA QT Interdisciplinary Review Team (QT-IRT) reviewed the PK, ECG, and safety data from SCY-078-106 and determined it was adequate to support QT assessment. The QT-IRT reviewer conducted a concentration-QTc analysis using the QTc data from 125 mg or 250 mg dose level (n=5, 1-hr infusion), 375 mg dose level (n=6, 1-hr infusion; n=2, 2-hr infusion), or placebo dosing (n=6). The study provided > 5-fold coverage for the therapeutic Cmax of 629 ng/mL and > 2-fold coverage for the worst case exposure scenario (geometric mean ratio of 2.52 in the presence of a strong CYP3A4 inhibitor, Table 8-38). The QT-IRT reviewer determined that the exposure achieved in the study supported waiving the requirement for a separate positive control.

Table 8-38. Change in QTcF by Ibrexafungerp Dose

Treatment	Plasma Ibrexafungerp Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI
Ibrexafungerp 125 mg, 1-hr IV	1,548	-2.3	(-4.1 to -0.4)
Ibrexafungerp 375 mg, 2-hr IV	2,128	-2.8	(-5.0 to -0.7)
Ibrexafungerp 375 mg, 1-hr IV	3,236	-3.9	(-6.9 to -1.0)

Ibrexafungerp 250 mg, 1-hr IV	3,489	-4.2	(-7.4 to -1.0)

Source: FDA QT-IRT review, Table 1, reformatted by clinical reviewer

There were no cardiac-related TEAEs during the study. No subjects had QT prolongation > 500 msec or increased > 60 msec over baseline following ibrexafungerp administration. Using a linear mixed-effects model approach, the slope of the relationship between plasma ibrexafungerp concentration and the change in QTcF was not statistically significant. Within the exposure range studied, the upper bound of the 90% CI for the predicted QTcF change was < 10 msec (Table 8-38).

- ***Reviewer comments:*** *At concentrations 5-fold higher than the concentrations achieved after a 1-day 300 mg BID treatment course of oral ibrexafungerp, ibrexafungerp did not prolong the QTc interval to any clinically relevant extent.*

Immunogenicity

Ibrexafungerp is a small molecule that is not expected to provoke a host immune response; therefore, immunogenicity was not specifically evaluated.

Additional Clinical Safety Tests

Upper Endoscopy
Given the findings of gastric mucosal degeneration in 28-day nonclinical studies of oral ibrexafungerp in rats and dogs, upper endoscopy and gastric biopsies were assessed in a cohort of 6 subjects receiving 800 mg of oral ibrexafungerp for 28 days and 2 subjects receiving placebo in one Phase 1 trial of oral ibrexafungerp (SCY-078-002). There were no gross findings on upper endoscopy examinations performed at the end of study treatment (Day 28±1). In 2 of the 6 ibrexafungerp-treated subjects, there were discrete reactive changes in the antrum pylori post-treatment that were not present pre-treatment. The Applicant assessed these changes as not clinically significant. None of the subjects had evidence of gastric mucosal degeneration.

Lower Extremity Ultrasound
Following the development of thrombotic events in a Phase 1 trial of IV ibrexafungerp, evaluations for lower extremity deep vein thrombosis (DVT) were added to a Phase 1 randomized, double-blind, placebo-controlled, cross-over, multiple dose trial evaluating safety and PK of oral ibrexafungerp administered at 750 mg BID x 2 days then 750 mg daily x 5 days in 16 subjects (SCY-078-111). There were no clinical signs of DVT or pulmonary emboli on targeted physical exams performed throughout the study period. No lower extremity DVTs were identified on ultrasound examinations performed at the end of study treatment (2 h after the last dose).

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Gastrointestinal Disorders

The most common adverse reactions in ibrexafungerp-treated subjects were gastrointestinal disorders. Using the Applicant's Gastrointestinal Disorders AESI flag, 32% of subjects experienced gastrointestinal disorders following a 1-day course of oral ibrexafungerp 300 mg BID compared to 14% of subjects administered placebo. Diarrhea (17%) was the most frequently reported gastrointestinal adverse reaction in the Phase 3 trials, followed by nausea (12%), abdominal pain (11%), and vomiting (2%). These reactions were self-limited and resulted in study discontinuation in only 1 subject. However, in the Phase 1 trials where higher doses oral ibrexafungerp were evaluated, the rates of diarrhea (52%), abdominal pain (31%), nausea (24%) and vomiting (11%) were substantially higher in the cohorts receiving multiple doses and resulted in more study discontinuations.

Degeneration of gastric mucosa and elevated plasma gastrin concentrations were observed in nonclinical studies of oral ibrexafungerp; therefore, additional clinical testing was performed to assess the gastric mucosa in early Phase 1 trials. The Applicant enlisted a consultant to review the gastrointestinal histology and plasma gastrin data from clinical and nonclinical studies (29 January 2015 report; IND 107521 SDN 0057). In 28-day oral ibrexafungerp toxicity studies in both rats and dogs, the consultant noted histologic changes consisting of loss of parietal cells and chief cells associated with disorganization, collapse and/or dilation of the mucosal glands. The magnitude of the effect was dose-dependent and reversible. Dose-dependent increases in plasma gastrin were observed but did not directly correlate with histologic findings. The histologic effects were also seen in a 7-day rat study (suggesting onset with < 7 days of dosing) and in IV studies (suggesting the mucosal degeneration was not due to a direct local effect).

In Phase 1 trials of oral ibrexafungerp, the consultant noted that gastrin levels were not significantly elevated and the one study with gastric biopsy data showed no evidence of mucosal degeneration post-treatment (SCY-078-002, 800 mg/day for 28 days). The SCY-078-002 trial achieved exposure levels that exceeded the NOAEL level in dogs in 5/6 subjects biopsied and the exceeded the effect level in dogs in 3/6 subjects biopsied. The consultant concluded that effects on gastric mucosa at the clinical dose levels would not have significant functional consequences and would be reversible.

In the Phase 3 trials, subjects were instructed to take study medication with a meal, but data on food intake in relationship to study drug administration was not collected. The Applicant proposed including a statement in the labeling that the frequency of nausea may be reduced when oral ibrexafungerp is taken with food, citing a Phase 1 trial of single dose oral ibrexafungerp 500 mg in the fed and fasted state (SCY-078-102). While the incidence of nausea was lower in the small number of subjects evaluated in the fed state (0/22) compared to the fasted state (4/24), the overall incidence of gastrointestinal reactions was similar between the two groups (7/22 fed, 9/24 fasted) and the number of subjects evaluated was too small to draw definitive conclusions about the mitigating effects of food on the incidence of nausea.

- ***Reviewer comments:*** *Gastrointestinal side effects, including abdominal pain, are common even with single day ibrexafungerp dosing used for the acute VVC Phase 3 trials. However, the gastric mucosal degeneration and elevated gastrin levels observed in the nonclinical studies were not seen at the oral ibrexafungerp doses evaluated in clinical trials.*

  The frequency of the GI adverse reactions appears to be dose-dependent. This observation suggests that gastrointestinal adverse reactions may be treatment-limiting for indications that require higher doses or longer durations of oral ibrexafungerp treatment than acute VVC.

8.2.5.2. Increased Transaminases

Transaminase elevations were identified as a potential safety signal in the early stages of oral ibrexafungerp clinical development. In the Phase 1 and Phase 2 trials, 8 subjects (1.5%) experienced elevated transaminase adverse events following oral ibrexafungerp administration and 2 of these events resulted in treatment discontinuation. In the Phase 3 trials, the Applicant pre-defined transaminase elevation as an event of clinical interest (ECI), with the definition requiring marked transaminase elevations ($\geq$ 8x ULN), sustained severe transaminase elevations ($\geq$5x ULN for > 2 wk), or severe transaminase elevations with other associated findings ($\geq$3x ULN with >2x ULN total bilirubin or clinical signs/symptoms). While 2 subjects met the ECI definition in Phase 1 trials, none of the subjects in the Phase 3 trials experienced transaminase elevations severe enough to meet the ECI definition.

Since the ECI definition was designed to capture the most severe transaminitis adverse events, the clinical reviewer also used the Drug-related Hepatic Disorders Standardized MedDRA Query (SMQ) to analyze TEAEs from the oral ibrexafungerp safety database for possible drug-related hepatotoxicity events with less severe transaminase elevations:

- In the Phase 3 trials, 5 subjects experienced events identified by the Drug-Related Hepatic Disorders narrow SMQ (4/545, 0.7% ibrexafungerp-treated and 1/275, 0.4% placebo-treated). All events were transaminase elevations, and none resulted in study discontinuation.

- In the Phase 2 trials, 6 subjects in the SCY-078-204 trial (5/153, 3.3% ibrexafungerp-treated and 1/32, 3.2% fluconazole-treated) and none in the SCY-078-203 trial experienced events identified by the Drug-Related Hepatic Disorders SMQ. All events were liver enzyme elevations, with one ibrexafungerp-treated subject experiencing an isolated GGT elevation and normal ALT and AST levels. None of the events resulted in study discontinuation.

- In the Phase 1 trials, 5 subjects experienced events identified by the Drug-Related Hepatic Disorders SMQ (4/298, 1.3% ibrexafungerp-treated, 1/16, 6.3% placebo). All events were transaminase elevations. Two of the ibrexafungerp-treated subjects discontinued the study due to these adverse events and in one of these subjects, the event was an SAE.

- ***Reviewer comments:*** *Transaminase elevations were observed following administration of oral ibrexafungerp in healthy volunteers and resulted in an SAE in one subject. Transaminase elevations were less frequent in the Phase 3 trials, but it is unclear if this is a function of limited testing (single liver safety laboratory assessment 10 days after dosing completed) or an actual decrease in incidence with the lower dose and duration of oral ibrexafungerp treatment used in the acute VVC trials. It is reassuring that all of the transaminitis adverse reactions reported in the safety database resolved and none were associated with elevations of bilirubin predictive of severe drug-induced liver injury (Hy's Law).*

8.2.5.3. Hypersensitivity

While hypersensitivity was not a common event in the oral ibrexafungerp clinical trials, two severe hypersensitivity reactions were reported in the studies submitted:

- A serious hypersensitivity reaction was reported in the oral ibrexafungerp-dabigatran DDI study (SCY-078-108). A 19 yo male developed fever, arthralgia, myalgias, lethargy, and a tender rash on the hands after 2 days of oral ibrexafungerp 750 mg BID. The reaction required hospital admission but responded to steroids. The clinical description was consistent with acute drug-induced febrile neutropenia (Sweet's syndrome) but no skin biopsy data were available to confirm the diagnosis.

- A severe hypersensitivity reaction was reported in the IV ibrexafungerp study submitted to the NDA as a cardiac safety study (SCY-078-106). A 31 yo woman developed flushing, chest tightness, headache, abdominal cramping, and jaw swelling minutes after starting an IV infusion of 125 mg ibrexafungerp in SBECD solution. She had tolerated a previous 30 mg IV ibrexafungerp dose. The reaction resolved within an hour following diphenhydramine administration.

The clinical reviewer used the Hypersensitivity SMQ to analyze TEAEs from the oral ibrexafungerp safety database for possible unrecognized hypersensitivity events:

- In the Phase 3 trials, there were no reported hypersensitivity reactions. Seven events were identified by the Hypersensitivity narrow SMQ, with similar incidence in the treatment arms (3 rash/dermatitis events in each arm and 1 facial swelling event in the placebo arm).

- In the Phase 2 trials, there were no events identified by the Hypersensitivity narrow SMQ in Study SCY-078-203. In Study SCY-078-204, there were 2 events identified (rash and eczema exacerbation) and both events occurred in ibrexafungerp-treated subjects.

- In the Phase 1 oral ibrexafungerp trials, the only hypersensitivity reaction was the previously described SAE. There were 9 other events identified by the Hypersensitivity narrow SMQ. All of the events were skin rashes and 5 of the 9 events occurred in a single study of 36 subjects evaluating drug-drug interactions between oral ibrexafungerp and dabigatran (SCY-078-108).

➢ ***Reviewer comments:*** *While hypersensitivity reactions were not reported in the Phase 3 trials, they appear to occur occasionally with ibrexafungerp administration and should be included in the labeling. Some of the rashes reported as adverse events in the oral ibrexafungerp safety database could be hypersensitivity reactions.*

(b) (4)

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(b) (4)

Overall, there were no reported DVTs or PEs in the oral ibrexafungerp safety database submitted with NDA 214900. The clinical reviewer used the Embolic and Thrombotic Events SMQ to analyze TEAEs from the oral ibrexafungerp safety database for possible unrecognized thrombotic events. The only event identified by the SMQ was thrombophlebitis in a subject in a Phase 1 trial of oral ibrexafungerp and pravastatin drug-drug interactions (SCY-078-115). The event was moderate severity and assessed as unrelated to study treatment.

- ***Reviewer comments:*** *There were no thrombotic events in the oral ibrexafungerp safety database. However, in the single oral ibrexafungerp study where thrombosis biomarkers were measured, elevations in D-dimer were observed in several subjects beginning ≥ 3 days after ibrexafungerp initiation. This finding, in combination with the DVT/PE events observed at the highest doses evaluated in a Phase 1 multiple ascending dose trial of IV ibrexafungerp, suggests a potential time- and/or dose-dependent thrombosis risk. Given the low dose (300 mg BID) and short duration (1-day), the risk appears to be minimal for the proposed acute VVC treatment dose.*

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

A Vulvovaginal Signs and Symptoms (VSS) score was used to evaluate efficacy and contributed to the data used by the investigators to identify adverse events in the Phase 3 trials. The clinical findings assessed by the score were consistent with the recommendations from the FDA guidance document *Vulvovaginal Candidiasis: Developing Drugs for Treatment*.[23] Clinical cure (primary efficacy endpoint) required full resolution of vulvovaginitis signs and symptoms. The vulvovaginal symptoms reported in the subject diaries were reviewed by the investigators to determine if any represented adverse events.

8.2.7. Safety Analyses by Demographic Subgroups

The incidence of treatment emergent adverse events in the pooled Phase 3 safety population by age, race, and ethnicity are summarized in **Table 8-39**. The Phase 3 trials did not include sufficient numbers of subjects aged 65 and over to determine whether TEAEs occurred more frequently in this population. The incidence of TEAEs appeared similar among subjects from different racial and ethnic groups enrolled in the Phase 3 trials.

Table 8-39 TEAE Incidence by Demographic Subgroup – Pooled Phase 3 Trials

[23] Ibid.

	Oral ibrexafungerp 300mg BID		Placebo BID	
	N	n(%)	N	n(%)
Age				
< 65 y	540	247 (45.7)	270	105 (38.9)
≥ 65 y	5	2 (40.0)	5	2 (40.0)
Race				
White	378	160 (42.3)	194	71 (36.6)
Black or African American	152	82 (53.9)	78	35 (44.9)
Asian	4	2 (50.0)	0	0
Other	11	5 (45.5)	3	1 (33.3)
Ethnicity				
Not Hispanic or Latino	445	185 (41.6)	236	88 (37.3)
Hispanic or Latino	100	64 (64.0)	39	19 (48.7)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Based on severe fetal malformations observed in animal studies, oral ibrexafungerp may cause fetal toxicity if administered to pregnant females (see Section 5.5 for detailed discussion).

Nonclinical Data
Rats and rabbits were evaluated in nonclinical embryo-fetal development studies of oral ibrexafungerp. When pregnant rats were administered oral ibrexafungerp doses of up to 50 mg/kg/day [5-times the recommended human dose (RHD) based on plasma AUC comparisons], no fetal malformations were observed. When pregnant rabbits were administered oral ibrexafungerp doses of 10, 25, or 50 mg/kg/day, fetal malformations were observed in the 25 mg/kg/day group (5-times RHD based on AUC comparison) and the 50 mg/kg/day group (13-times RHD based on AUC comparison). Malformations present in a single animal in the 25 mg/kg/day group included absent ear pinna, general body craniorachischisis, trunk kyphosis, absent hindpaw, and forelimb phocomelia. Malformations including absent hindpaw, and anencephaly occurred with an increased litter incidence in the high-dose group of 50 mg/kg/day (approximately 13 times the RHD based on AUC comparison) as well as other malformations that occurred in single litters but not in the control groups including absent ear pinna, exencephaly, forelimb phocomelia, and absent thyroid gland. The occurrence of these

malformations in the mid-dose and high-dose oral ibrexafungerp groups but not in the concurrent control groups or historical control data strongly suggests a drug-related effect.

Clinical Data

No studies have investigated the safety of oral ibrexafungerp in pregnant women. The Phase 3 trial protocols required subjects to be not pregnant, not lactating, and highly unlikely to become pregnant. Women of reproductive potential were required to use effective contraception (intrauterine device or hormonal contraceptives) $\geq$ 30 days prior to the baseline visit through 10 days after completion of study treatment or to agree to remain abstinent or use a barrier contraceptive method from the time of consent through 10 days after completion of study treatment.

In the oral ibrexafungerp safety database, 4 subjects had positive pregnancy tests within 5 weeks of drug exposure (**Table 8-40**). All subjects had negative urine pregnancy tests at screening visits within 2 days prior to starting ibrexafungerp. Three of these subjects had positive pregnancy tests within 7-10 days of their last ibrexafungerp dose. The fourth subject had a positive pregnancy test approximately one month after the last ibrexafungerp dose. One subject electively terminated the pregnancy in the first trimester; the other three subjects delivered healthy infants with no reported complications.

There are no reports of ibrexafungerp use by lactating women. There are no data on the presence of ibrexafungerp in human milk, effects on the breast-fed infant, or effects on milk production.

- ***Reviewer comments:*** *Available clinical data on oral ibrexafungerp use in pregnant women are insufficient to draw conclusions about any drug-associated risks of birth defects, miscarriages, or adverse maternal or fetal outcomes. However, the findings of phocomelia, anencephaly and other malformations in the rabbit embryo-fetal study suggest a drug-related toxicity.*

  Since VVC is a non-life-threatening infection with alternative approved treatments and severe malformations were observed in the rabbit embryo-fetal toxicity studies at exposures < 25-fold the human exposures at the MRHD with an NOAEL at exposures < 10-fold the human exposure at the MRHD, the risk-benefit ratio does not support use in pregnant women. A contraindication for use in pregnancy will be included in the labeling. Providers will be advised to verify pregnancy status for females of reproductive potential prior to oral ibrexafungerp treatment and recommend use of effective contraception during treatment and for 4 days after the last dose. The Applicant will conduct a single-arm pregnancy safety study to collect data from women incidentally exposed to oral ibrexafungerp during pregnancy as a postmarketing requirement (PMR).

  Since there are no data on the use of oral ibrexafungerp in animals or humans and the drug is anticipated to be used in females of reproductive potential, the Applicant will conduct a milk only clinical lactation study as a PMR.

Table 8-40 Pregnancies Reported After Ibrexafungerp Exposure -- All Trials

Trial	Subject	Oral Ibrexafungerp Dosing	Date(s) of Treatment	Last Menstrual Period	Baseline Pregnancy Test	Date of Positive Pregnancy Test	Pregnancy Outcome
SCY-078-204	Subject ID (b) (6) 24 yo Black, not Hispanic or Latino female	150 mg BID x 3 d (total dose 1800 mg)	Days 1-3 (b) (6)	Not reported	Screening urine pregnancy test negative *(date not reported, other screening tests* (b) (6)	Day 11 (b) (6) pregnancy reported	Live birth Healthy male infant, no known birth defects
SCY-078-303	Subject ID (b) (6) 24 yo White Hispanic or Latino female	300 mg BID x 1 d (total dose 600 mg)	Day 1-2 (b) (6)	(b) (6)	Day 1 (b) (6) urine pregnancy test negative	Day 12 (b) (6) positive urine pregnancy test	Live birth Healthy female infant No delivery or newborn complications reported
SCY-078-303	Subject ID (b) (6) 27 yo White not Hispanic or Latino female	300 mg BID x 1 d (total dose 600 mg)	Day 1-2 (b) (6)	(b) (6)	Day 1 (b) (6) urine pregnancy test negative	Day 35 (b) (6) positive home urine pregnancy test post-study completion	Live birth Vacuum-assisted delivery No newborn complications reported
SCY-078-306	Subject ID (b) (6) 29 yo Black not Hispanic or Latino female	300 mg BID x 1 d (total dose 600 mg)	Day 1-2 (b) (6)	(b) (6)	Day -2 (b) (6) urine pregnancy test negative	Day 12 (b) (6) positive urine pregnancy test at unscheduled visit	Elective termination of pregnancy Day 27 (b) (6)

Source: Clinical reviewer

Pediatrics and Assessment of Effects on Growth

The Applicant is seeking an indication for oral ibrexafungerp for treatment of acute VVC in (b) (4) adults. Since *Candida* sp. are rarely a cause of vaginitis in pre-pubertal girls, the Agreed Initial Pediatric Study Plan (Agreed iPSP) for treatment of VVC includes a partial waiver for age < 12 years old. Juvenile animal studies were not conducted because the Applicant did not plan to study oral ibrexafungerp in pre-pubertal children.

The Applicant intended to enroll postmenarchal adolescent girls ≥ 12 years old in the Phase 3 acute VVC treatment trials. However, only a single adolescent was enrolled, and this subject was randomized to the placebo arm. During the review cycle, the Applicant completed a PK and safety study enrolling 10 adolescent girls who received oral ibrexafungerp with the proposed VVC treatment regimen of 300 mg BID x 1 day. Summary safety data from this study was submitted and used in the safety assessment. The rationale for use of the data from trials conducted in adult women in combination with summary safety data from a PK study in adolescents to support an indication for oral ibrexafungerp treatment of acute VVC in adolescent girls is discussed in Section 10 *Pediatrics*.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reports of ibrexafungerp overdose to date. There is no known abuse potential for ibrexafungerp.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ibrexafungerp has not been granted marketing approval in any country.

Expectations on Safety in the Postmarket Setting

The use of oral ibrexafungerp at a dose of 300 mg BID x 1 day in non-pregnant postmenarchal females does not present significant safety concerns for the postmarket setting. If oral ibrexafungerp is used off-label at higher doses or for longer durations, the most likely result will be increased frequency of gastrointestinal adverse events. Other potential issues with use of higher doses or longer durations of oral ibrexafungerp are transaminase elevations and thrombotic events. The Applicant has multiple ongoing studies for other indications (prevention of recurrent VVC, treatment of invasive fungal diseases) that will yield additional data to define these risks.

Given the risk of fetal toxicity identified by the nonclinical studies in rabbits, a contraindication for use in pregnancy will be added to the label and healthcare providers will be advised to verify pregnancy status in females of reproductive potential prior to initiating oral ibrexafungerp therapy. The Applicant will conduct a single-arm pregnancy safety study using a structured approach to data collection to obtain follow-up data on all ibrexafungerp-exposed pregnancies

identified.

8.2.11. Integrated Assessment of Safety

The data from women receiving oral ibrexafungerp for treatment of acute VVC in the Phase 3 trials (VANISH-303 and VANISH-306) form the basis of the safety assessment. While gastrointestinal adverse events were common in these patients, treatment discontinuations due to adverse reactions were infrequent. There were no SAEs related to oral ibrexafungerp treatment in the Phase 3 trials and there were no deaths.

Gastrointestinal adverse reactions, most commonly diarrhea, nausea, and abdominal pain, occurred frequently with administration of oral ibrexafungerp 300 mg BID for 1 day in the Phase 3 trials. Early in the ibrexafungerp development program, non-clinical findings of gastric mucosal degeneration prompted additional safety testing. However, when healthy volunteers were exposed to a substantially higher oral ibrexafungerp dose and treatment duration (800 mg daily x 28 d) than the proposed VVC treatment dose, there were no signs of gastric mucosal degeneration on endoscopy. In the Phase 3 VVC treatment trials, gastrointestinal adverse reactions were usually mild and resolved in < 3 days. (b) (4) The frequency of the gastrointestinal adverse reactions appears to be dose-dependent and may be treatment-limiting for indications requiring higher doses or longer durations of oral ibrexafungerp therapy.

Transaminase elevations were identified as oral ibrexafungerp adverse reactions in the Phase 1 trials, resulting in treatment discontinuation in 2 healthy volunteers. Transaminase elevations were less frequent in the Phase 3 VVC treatment trials, but this may have been partly the result of the trial design that performed safety laboratory testing at a single timepoint 10 days after dosing completion. There were no Hy's Law cases in the safety database and transaminitis was reversible in all subjects. Given that oral ibrexafungerp treatment for VVC is a single day therapy, transaminase levels do not need to be monitored with treatment.

Hypersensitivity reactions after oral ibrexafungerp administration were infrequently identified. However, one Phase 1 study participant required hospitalization and steroid therapy for a hypersensitivity reaction. It is possible that some of the rashes reported as adverse events in the safety database may have also represented hypersensitivity reactions; therefore, hypersensitivity reaction will be included in the labeling as a less common adverse reaction.

The potential for a dose-dependent association of ibrexafungerp with thrombotic events remains an unresolved issue. DVT and/or PE were observed in the highest dose cohorts in a multiple ascending dose trial of IV ibrexafungerp, prompting a full clinical hold on the IV ibrexafungerp IND. However, there were no thrombotic events in the oral ibrexafungerp safety database. It is possible that the thromboses observed in the IV ibrexafungerp trial were due to an irritant effect of the drug on the vasculature. Alternatively, ibrexafungerp could have intrinsic pro-thrombotic properties that pose a time- or dose-dependent risk. The latter

explanation is suggested by the elevated D-dimer concentrations observed after ≥ 3 days of oral ibrexafungerp dosing (750 mg BID x 2 d then 750 mg daily). At the dose proposed for acute VVC treatment (300 mg BID x 1 d), the thrombotic risk appears minimal. If higher doses and longer durations of oral ibrexafungerp therapy are explored, D-dimer measurements may be indicated.

Given the severe fetal malformations observed in rabbits exposed to oral ibrexafungerp at 5-13 times the RHD, the oral ibrexafungerp labeling will contain a contraindication for use in pregnancy with the recommendation to verify pregnancy status and advise use of effective contraception during treatment and for 4 days after the last dose in females of reproductive potential.

Oral ibrexafungerp exhibits an acceptable safety profile for treatment of acute VVC in non-pregnant women. The risks of a single-day course of oral ibrexafungerp 300 mg BID primarily consists of gastrointestinal adverse reactions that are mild and short-lived. The safety data also support the use of oral ibrexafungerp for treatment of VVC in postmenarchal adolescents (see Section 10 *Pediatrics*).

8.3. Statistical Issues

There are no major statistical issues.

As discussed in Sections 8.1.1 and 8.1.2 under Analysis Populations, the clinical study report for Study 306 reported the efficacy results based on a revised definition from that stated in the SAP for the mITT population. Although not mentioned for Study 303, it was found that the same definition for the mITT population was also used in the clinical study report for Study 303. Even though the change in definition affected only 2 subjects in each treatment group in Study 303, 1 subject in the ibrexafungerp group and 5 subjects in the placebo group in Study 306, and there was no impact on the overall results, the revision to the definition of the mITT was not accepted by the Division. Therefore, the SAP definition of the mITT population was used for all analyses presented in this review and will be the one recommended for presentation of the results in Section 14 of the product label.

8.4. Conclusions and Recommendations

VANISH-303 and VANISH-306 were adequate and well-controlled trials that showed statistical superiority of ibrexafungerp over placebo in clinical cure of VVC at the TOC visit (Day 8-14). The data meet the evidentiary standard of effectiveness and demonstrate a clinically meaningful improvement in outcomes for women with VVC treated with oral ibrexafungerp. Safety data from these two Phase 3 trials along with supportive data from Phase 1 and 2 trials demonstrate the safety of oral ibrexafungerp 300 mg BID x 1 day for VVC treatment. The adverse reactions observed were primarily gastrointestinal symptoms that were mild and short duration. Since severe fetal malformations were observed in rabbit studies at exposures < 25-fold the human

exposures at the MRHD with an NOAEL at exposures < 10-fold the human exposure at MRHD, VVC is a non-life-threatening infection and other effective treatment options are available for VVC treatment, oral ibrexafungerp use will be contraindicated in pregnant women. The reviewers recommend approval of oral ibrexafungerp for treatment of VVC in postmenarchal females.

9 Advisory Committee Meeting and Other External Consultations

Since there were no specific issues that needed input from external experts, an advisory committee meeting was not convened for this NDA.

10 Pediatrics

The Applicant is seeking an indication for oral ibrexafungerp for treatment of acute VVC in (b) (4) adults and has requested a partial waiver of pediatric assessments for children < 12 y. The pediatric development plan for treatment of VVC was influenced by the epidemiology of VVC, which occurs at a very low incidence in pre-pubertal girls, and the challenges encountered enrolling post-pubertal girls in the Phase 3 trials of oral ibrexafungerp for VVC treatment.

VVC in Pre-Pubertal Girls

VVC is an uncommon cause of vulvovaginitis in pre-pubertal girls. In published studies evaluating vaginal fluid cultures from pediatric patients, *Candida* species were rarely isolated in cultures obtained from pre-pubertal girls (Table 10-1). These findings support the Applicant's request for a waiver of pediatric assessments in younger children since antifungal therapies such as ibrexafungerp would be not be required to treat vulvovaginitis in this population under most circumstances.

Table 10-1 Studies Evaluating Incidence of *Candida* sp. in Samples From Pediatric Patients

Citation	Study Population	*Candida* sp. Incidence	Reviewer Comments
Yilmaz et al (2012)[24]	Retrospective single center study of 112 girls with vulvovaginitis: 72 pre-pubertal (mean age 5.5±2.1 y) 40 pubertal (≥Tanner Stage II; mean age 16.3±2.3 y)	Pre-pubertal: 1/72 (1.4%) Pubertal: 11/40 (28%)	Most common isolate in pre-pubertal girls: Group A streptococcus Most common isolate in pubertal girls: *C. albicans*
Banerjee et al (2004)[25]	Retrospective study of genital tract specimens submitted to single laboratory center from children < 12 y	Overall incidence 22/379 (6%) samples from girls <12 y • 13 from girls <3 y • 4 from postmenarchal girls	Authors note incidence of *Candida* sp. <1% in samples from pre-pubertal girls 3-9 y; higher incidence prior to toilet-training and after menarche

[24] Yilmaz, A. E., et al. (2012). "Comparison of clinical and microbiological features of vulvovaginitis in prepubertal and pubertal girls." J Formos Med Assoc **111**(7): 392-396.
[25] Banerjee, K., et al. (2004). "Low prevalence of genital candidiasis in children." Eur J Clin Microbiol Infect Dis **23**(9): 696-698.

Jaquiery et al (1999)[26]	Case-control study of 50 pre-menarchal girls > 2 y with vulvovaginitis presenting to pediatric hospital clinics or gynecology clinic	Cases: 1/50 (2%) Controls: 0/50	Isolates from vaginal cultures similar in both groups, predominately anaerobes, diphtheroids, and coagulase negative staphylococci
Pierce et al (1992)[27]	Prospective study of 200 girls 1-15 y with vulvovaginitis (160 with vaginal fluid culture)	Overall incidence 7/160 (4%) samples from girls 1-15 y • 2 from girls <2 y • 4 from pubertal girls	Single *Candida* sp. isolate in a pre-pubertal girl > 2 y was from a patient with lichen sclerosis
Paradise et al (1982)[28]	Case-control single center study of 54 pre-menarchal girls 5 months - 12 y with vulvovaginitis (52 with vaginal fluid culture): 36 pre-pubertal 16 pubertal (≥Tanner Stage II)	Cases: Pre-pubertal: 0/36 Pubertal: 8/16 (50%) Controls (matched for age and Tanner Stage): 0/50	Authors note high incidence of *Candida* sp. isolated from pubertal but pre-menarchal girls not previously reported

Source: Clinical reviewer

VVC in Post-Pubertal Girls

The incidence of VVC as a cause of vulvovaginitis increases after puberty as the result of hormonal influences on the vaginal microenvironment. In the low estrogen environment prior to puberty, the vaginal flora is predominated by anaerobic flora that inhibit the growth of *Candida* species.[29] With the onset of puberty, estrogen stimulation of the vaginal mucosa causes increased glycogen concentration, which in turn promotes colonization by lactobacilli.[30] Lactobacilli metabolize glycogen to lactic acid, resulting in the lower vaginal pH (<4.5) also found in healthy pre-menopausal women.

Extrapolation of Data from Adults to Adolescents

The Applicant planned to enroll adolescent girls (≥12 y) in the Phase 3 trials evaluating oral ibrexafungerp for treatment of acute VVC, estimating that 10 adolescent girls would be randomized in each trial. However, only one adolescent was enrolled in the Phase 3 program (VANISH-303 placebo arm). Given the expected similarities in disease characteristics, dosing,

[26] Jaquiery, A., et al. (1999). "Vulvovaginitis: clinical features, aetiology, and microbiology of the genital tract." Arch Dis Child **81**(1): 64-67.
[27] Pierce, A. M. and C. A. Hart (1992). "Vulvovaginitis: causes and management." Ibid. **67**(4): 509-512.
[28] Paradise, J. E., et al. (1982). "Vulvovaginitis in premenarcheal girls: clinical features and diagnostic evaluation." Pediatrics **70**(2): 193-198.
[29] Banerjee, K., et al. (2004). "Low prevalence of genital candidiasis in children." Eur J Clin Microbiol Infect Dis **23**(9): 696-698.
[30] Agana, M. G., et al. (2019). "Vulvovaginitis in adolescents." Pediatric Medicine **2**.

and PK, the Applicant is proposing to use efficacy and safety data from trials of oral ibrexafungerp for treatment of acute VVC in adults to support approval for treatment in adolescents.

The extrapolation of efficacy data is supported by the similarities in the natural history of VVC in post-pubertal girls and in women. The increased estrogen levels of puberty result in a shift to a vaginal microenvironment similar to that observed in adults, with an increased presence of lactobacilli in the vaginal flora and a reduction in vaginal pH. These conditions support colonization by *Candida* spp., and the yeast species colonizing adolescents and adults are not expected to differ.

While oral ibrexafungerp pediatric PK data were not submitted with the NDA, there are no anticipated changes in the local tissue distribution of ibrexafungerp in post-pubertal girls compared to adult women. Since the drug target is a fungal enzyme and the VVC disease process is the same in post-pubertal girls and adults, the concentrations required for ibrexafungerp antimicrobial activity will not differ between these populations.

The safety of oral ibrexafungerp dosed at 300 mg BID x 1 day is not expected to differ in post-pubertal adolescents and adults. There were no serious adverse reactions attributable to ibrexafungerp in the Phase 3 trials of acute VVC treatment. The most common adverse events were gastrointestinal effects which do not pose a greater risk to adolescents than adults. The Applicant submitted summary safety data from a recently completed open-label PK study enrolling adolescents 12-17 y with vaginitis who received oral ibrexafungerp 300mg BID x 1 day (SCY-078-120). Four subjects were enrolled in Cohort A (12-14 y); none experienced TEAEs. Six subjects were enrolled in Cohort B (15-17 y); two subjects experienced mild, self-limited gastrointestinal adverse reactions that were consistent with the adverse reactions reported in the Phase 3 trials. The existing safety data support approval of oral ibrexafungerp for treatment of VVC in postmenarchal adolescents.

- ***Reviewer comments:*** *Since Candida sp. are a rare cause of vaginitis in pre-pubertal girls, the clinical reviewer supports the Applicant's request for a partial waiver of pediatric assessment for children <12 y.*

  Since the natural history of VVC is similar in post-pubertal girls and adults and there are no expected differences in PK, the efficacy of oral ibrexafungerp for treatment of VVC in adults can be extrapolated to post-pubertal girls. Since the adverse reactions associated with the 1-day 300 mg BID oral ibrexafungerp are not expected to pose a greater risk to adolescents and preliminary data from a PK study enrolling 10 adolescents confirms that the adverse reaction profile is similar to adults, the safety data support the use of oral ibrexafungerp for treatment of VVC in adolescents. The Applicant will submit the full clinical study report from the adolescent PK study (SCY-078-120) and proposed labeling updates as a postmarketing commitment.

Because the incidence of VVC as a cause of vulvovaginitis increases with post-pubertal estrogen changes, the reviewer recommends removing references to age from the oral ibrexafungerp labeling recommendations and using "postmenarchal females" or "postmenarchal adolescents and adults" to define the target population.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The prescribing information (PI) was revised to add a contraindication (section 4) for use in pregnant women and a warning (section 5) for fetal toxicity based on severe fetal malformations observed in animal studies. Healthcare providers are advised to verify pregnancy status in females of reproductive potential prior to initiating ibrexafungerp and recommend use of effective contraception during treatment and for 4 days after the last dose. This was added to several sections/subsections throughout the PI.

In Section 6 ADVERSE REACTIONS of the proposed PI the following changes are recommended:

Table 11-1 summarizes the clinical reviewer's recommended revisions to the table summarizing common treatment-related adverse reactions in Section 6 Adverse Reactions of the proposed labeling. The recommendations include a cutoff of 2% (b) (4) for the adverse reaction table and revised adverse reaction incidence with more inclusive coding of terms for abdominal pain and dizziness (see Section 8.2.3 *Adequacy of Applicant's Clinical Safety Assessments*).

Table 11-1 Proposed Revisions to Common Adverse Reactions Table in Ibrexafungerp PI

Adverse Reactions with Rates ≥ (b) (4) % in BREXAFEMME-Treated Patients

(b) (4) ***Adverse Reaction***	**BREXAFEMME** N = 545 n (%)	**Placebo** N = 275 n (%)
(b) (4)		
Diarrhea	91 (16.7%)	9 (3.3%)
Nausea	65 (11.9%)	11 (4.0%)
Abdominal pain[1]	(b) (4) *62 (11.4%)*	(b) (4) *14 (5.1%)*
Dizziness[2]	*18 (3.3%)*	*7 (2.5%)*
Vomiting	*11 (2.0%)*	*2 (0.7%)*

[1] Includes abdominal pain, abdominal pain upper, (b) (4) abdominal pain lower, and abdominal discomfort
[2] Includes dizziness and postural dizziness

The clinical reviewer also recommends adding the following text to report less frequent ibrexafungerp adverse reactions:

> *Adverse reactions occurring in < 2% of patients receiving BREXAFEMME in Trial 1 and Trial 2: dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, rash/hypersensitivity*

The rationale for inclusion of these TEAEs as adverse reactions is summarized in Table 8-33 (Section 8.2.4 Safety Results).

Additional labeling recommendations from the reviewers include:

In Section 2 DOSAGE AND ADMINISTRATION of the proposed PI the following changes are recommended:

- Include a recommendation for dosage reduction of 150 mg twice daily for one day in patients with concomitant use of a strong inhibitor of cytochrome P450 isoenzymes.

In Section 7 DRUG INTERACTIONS of the proposed PI the following changes are recommended:

- Include a recommendation to reduce the BREXAFEMME dosage with concomitant use of strong CYP3A inhibitors and avoid concomitant administration with strong and moderate CYP3A inducers under the effect of coadministered drugs on ibrexafungerp pharmacokinetics.
- Delete information pertaining to the effect of ibrexafungerp on the pharmacokinetics of coadministered drugs as the exposure changes from these studies were not considered clinically significant at the approved recommended dosage for VVC.

In Section 8 USE IN SPECIFIC POPULATIONS of the proposed PI the following changes are recommended:

- Include specific information regarding the administered doses and the days of administration for ibrexafungerp and identification of the ibrexafungerp NOAEL and/or LOAEL values in each nonclinical study.
- Describe the serious fetal malformations associated with ibrexafungerp administration in the rabbit embryo-fetal study at dose exposures ≥ 5 times the recommended human dose (RHD) with a NOAEL dose of approximately 2 times the RHD.
- Include a contraindication for administration of BREXAFEMME in pregnancy in the Risk Summary of Subsection 8.1.
- Include information on how to report cases to the drug manufacturer's pregnancy safety study for pregnant women exposed to BREXAFEMME and their healthcare providers in Subsection 8.1 and Section 17.
- In Section 8.3 include the following: BREXAFEMME may cause fetal harm when administered to a pregnant female; Verify pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME; and females of reproductive potential are advised to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.
- Revise Section 8.4 to include the following: The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. Use of BREXAFEMME in post-menarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional safety data from post-menarchal pediatric females

- Add conclusion of no significant difference in exposures between elderly and young subjects based on the dedicated pharmacokinetic/pharmacodynamic study in geriatric patients to Subsection 8.5 pursuant to 21.CFR.201.57.

In Section 12 CLINICAL PHARMACOLOGY of the proposed PI the following changes are recommended:

- Add a statement regarding the unknown exposure-response relationship and time course of pharmacodynamic response to Subsection 12.2 pursuant to 21 CFR 201.57.
- Numerous editorial and formatting changes to improve readability (e.g., revise or remove subheadings, qualify the caloric composition of a high fat meal, specify the activity of the metabolite and remove extraneous information such as repeated pharmacokinetic information or doses that are expected to apply to the recommended dosage for VVC).
- Describe the primary route of elimination of ibrexafungerp as biliary excretion and metabolism rather than metabolism alone. While the Applicant's ADME study suggests fecal recovery is the result of biliary elimination following systemic absorption rather than excretion of unabsorbed drug, metabolism cannot be excluded given the unknown fraction of absorbed drug and increase in exposure noted in the clinical drug interaction study with the strong CYP3A4 inhibitor ketoconazole.
- Qualify the primary oxidation reaction observed in vitro as hydroxylation by CYP3A4.
- In Subsection 12.4, edit the "first list" and "second list" of microorganisms based on data from the clinical trials and in vitro data.

In Section 13 NONCLINICAL TOXICOLOGY of the proposed PI the following changes are recommended:

- Include specific information regarding the administered doses and the days of administration for ibrexafungerp and identify the ibrexafungerp NOAEL values for male and female rats in the fertility study.

In Section 14 CLINICAL STUDIES of the proposed PI, the following changes are recommended:

- When describing the studies, the statement (b) (4) should be deleted. (b) (4)
- The MITT population should be defined based on the SAP stated definition and all values reported in Section 14 should be based on that population.
- Due to differences in study populations, the demographic information should be described for each study separately.
- In the table summarizing the efficacy results, differences in proportions and corresponding 95% confidence intervals should be presented (b) (4) should be removed and complete clinical response at follow-up

should be presented. Table 11-2 is the recommended table to be included in Section 14.

Table 11-2: Proposed Table for Section 14 of Ibrexafungerp PI

Clinical and Mycological Response, MITT Population

	Trial 1		Trial 2	
	BREXAFEMME N = 190 n (%)	**Placebo N = 100 n (%)**	**BREXAFEMME N = 189 n (%)**	**Placebo N = 89 n (%)**
Complete Clinical Response at TOC[1]	95 (50.0)	28 (28.0)	120 (63.5)	40 (44.9)
Difference (95% CI)	22.0 (10.2, 32.8)		18.6 (6.0, 30.6)	
P-value	0.001		0.009	
Negative Culture at TOC	94 (49.5)	19 (19.0)	111 (58.7)	26 (29.2)
Difference (95% CI)	30.5 (19.4, 40.3)		29.5 (17.2, 40.6)	
P-value	< 0.001		< 0.001	
Complete Clinical Response at follow-up[2]	113 (59.5)	44 (44.0)	137 (72.5)	44 (49.4)
Difference (95% CI)	15.5 (3.4, 27.1)		23.1 (10.8, 35.0)	
P-value	0.007		0.006	

[1]Absence of signs and symptoms (VSS Score of 0) without need for additional antifungal therapy or topical drug therapy for the treatment of vulvovaginal symptoms at test of cure (TOC) visit.
[2]Absence of signs and symptoms (VSS Score of 0) without need for further antifungal treatment or topical drug therapy for the treatment of vulvovaginal symptoms prior to follow-up visit.

In Section 17 PATIENT COUNSELING INFORMATION of the proposed PI, the following changes are recommended

- Add a section on risk of fetal toxicity that includes instructions to inform their healthcare provider of a known or suspected pregnancy and encourage reporting of pregnancies to the drug manufacturer's pregnancy safety study
- Make the following revisions in the Important Administration Instructions:
  - Inform the patient that each BREXAFEMME dose consists of two tablets. A total treatment course is two doses taken approximately 12 hours apart and consists of a total of four tablets.
  - If the first two tablets are taken in the morning, the second two tablets should be taken that same day in the evening. If the first two tablets are taken in the afternoon or evening, the second two tablets should be taken the following morning.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended. The risks associated with oral ibrexafungerp will be communicated in the labeling.

13 Postmarketing Requirements and Commitment

The Applicant has agreed to the following postmarketing requirements:

Conduct a worldwide single-arm descriptive study that collects prospective and retrospective data in women exposed to Brexafemme (ibrexafungerp) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. Proposed milestone schedule:

Draft protocol submission: 12/31/2021
Final protocol submission: 6/30/2022
Interim study report: 6/30/2023
Interim study report: 6/30/2024
Interim study report: 6/30/2025
Interim study report: 6/30/2026
Interim study report: 6/30/2027
Interim study report: 6/30/2028
Study completion: 6/30/2029
Final study report submission: 12/31/2029

Perform a milk-only lactation study in lactating women receiving therapeutic doses of Brexafemme (ibrexafungerp) to assess the concentrations of ibrexafungerp in breast milk using a validated assay. Proposed milestone schedule:

Draft protocol submission: 1/30/2022
Final protocol submission: 7/31/2022
Study completion: 7/31/2024
Final study report submission:1/30/2025

The Applicant has agreed to the following postmarketing commitment:

Submit the final clinical study report for the oral ibrexafungerp adolescent pharmacokinetic study (SCY-078-120). Proposed schedule:

Study completion: Completed
Final report submission: 11/2021

14 Division Director (Clinical) Comments

I agree with the review team's assessment and recommendations.

15 Office Director (or designated signatory authority) Comments

I agree with the review team's assessment and recommendations.

16 Appendices

16.1. References

References provided as footnotes on the pages cited.

16.2. Financial Disclosure

The Applicant provided a list of the 70 clinical investigators at the study sites activated globally in the two Phase 3 covered clinical trials (VANISH-303 and VANISH-306). The Applicant certified that they had not entered into any financial arrangements with the listed investigators whereby the value of the compensation could affect the outcome of the trial. None of the investigators had a proprietary interest in the product, had significant equity in the sponsor, or had received significant payments of other sorts as defined in 21 CFR part 54.

Covered Clinical Study #1: SCY-078-303 (VANISH-303)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 28		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ n/a	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ n/a	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ n/a	No ☐ (Request explanation from applicant)

Covered Clinical Study #2: SCY-078-306 (VANISH-306)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 42		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: n/a Significant payments of other sorts: n/a Proprietary interest in the product tested held by investigator: n/a Significant equity interest held by investigator in sponsor of covered study: n/a		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ n/a	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ n/a	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ n/a	No ☐ (Request explanation from applicant)

16.3. Clinical Microbiology

The spectrum of ibrexafungerp in vitro activity was evaluated against a panel of clinically relevant yeast isolates. The minimum inhibitory concentrations (MIC) were determined by the broth microdilution method and results were reported after 24 hours at 37°C determined for prominent inhibition (MIC-50 or 50% inhibition of growth compared to growth control) in accordance with CLSI M27-A3 guidelines. The isolates represent clinical *Candida* spp. obtained between 2008 and 2020 across multiple centers in the United States and European Union. **Table 16-1** summarizes the activity of ibrexafungerp across the studies submitted in the NDA, with MIC values ranging from ≤0.007 – > 4 µg/mL against *Candida* spp. *Candida albicans* showed the lowest MIC with MIC_{90} values ranging from 0.06 - 1 µg/mL depending on the study. The highest ibrexafungerp MIC_{90} values were observed against *C. krusei* (1 – 4 µg/mL), *C. guillermondii* (4 µg/mL), *C. orthopsilosis* (4 µg/mL) and *C. lusitaniae* (4 µg/mL). Against *C. glabrata,* ibrexafungerp MIC_{90} values ranged 0.25 – 4 µg/mL. Similarly, the ibrexafungerp MIC_{90} values ranged from 0.5 – 1 µg/mL.

Table 16-1. Activity of ibrexafungerp against *Candida* isolates (Surveillance Studies)

Organism	N	Range	MIC50	MIC90	Reference
C. albicans	**404**	**≤0.007 - 2**	**≤0.03 – 0.5**	**0.06 – 1**	**ALL STUDIES**
	32		0.008	0.025	PD002
	33	0.06 – 0.25	0.06	0.12	SCY078-MB-003
	99	0.016 – 2	0.25	1	SCY078-MB-015
	69	0.03 – 2	0.12	0.25	SCY078-MB-006
	10	0.03 – 1	--	0.125	SCY078-MB-021
	29	0.06 – 2	0.12	1	Pfaller (2013)
	10	≤0.03 – 0.05	≤0.03	--	Jimenez-Ortigosa (2014)
	8	0.25 – 2	0.25 – 0.5	--	Borroto-Esodal (2016)
	55	≤0.007 – 1	0.03	0.06	Marcos-Zambrano (2017)
	33	0.06 – 0.25	0.06	0.12	Schell (2017)
	16	0.03 – 0.125	--	--	Arendrup (2020)
C. glabrata	**312**	**0.125 – 16**	**0.125 – 1**	**0.25 – 4**	**ALL STUDIES**
	15		0.125	0.25	PD002
	23	0.25 – 1	0.25	1	SCY078-MB-003
	72	0.125 – 2	1	1	SCY078-MB-015
	67	0.12 – 16	0.5	4	SCY078-MB-006
	10	0.25 – 0.5	--	0.5	SCY078-MB-021
	29	0.5 – 2	0.5	2	Pfaller (2013)
	9	0.12 – 0.5	0.12	--	Jimenez-Ortigosa (2014)
	17	0.5 – 2	1	2	Borroto-Esodal (2016)
	31	0.015 – 2	0.125	0.5	Marcos-Zambrano (2017)
	23	0.25 – 1	0.25	0.25	Schell (2017)
	16	0.25 – 0.5	--	--	Arendrup (2020)
C. krusei	**130**	**0.015 – 4**	**0.5 – 1**	**1 – 2**	**ALL STUDIES**
	18		1	1	PD002
	6	0.5 – 4	--	--	SCY078-MB-003
	14	0.25 – 2	1	2	SCY078-MB-015
	34	0.25 – 4	1	2	SCY078-MB-006
	10	1	1	1	SCY078-MB-021
	19	0.5 – 2	0.5	2	Pfaller (2013)
	11	0.25 – 0.5	0.5	--	Jimenez-Ortigosa (2014)
	12	0.015 – 1	0.5	1	Marcos-Zambrano (2017)
	6	0.5 – 4	--	--	Schell (2017)
C. parapsilosis	**220**	**0.03 – 8**	**0.06 – 1**	**0.125 – 2**	**ALL STUDIES**
	22		0.06	0.125	PD002

Organism	N	Range	MIC50	MIC90	Reference
	19	0.25 – 0.5	0.25	0.25	SCY078-MB-003
	41	0.125 – 2	1	2	SCY078-MB-015
	43	0.12 – 4	0.5	1	SCY078-MB-006
	10	0.25 – 1	--	1	SCY078-MB-021
	15	0.25 – 1	0.5	2	Pfaller (2013)
	19	0.25 – 8	0.5	--	Jimenez-Ortigosa (2014)
	33	0.03 – 0.5	0.25	0.5	Marcos-Zambrano (2017)
	18	0.25 – 0.5	0.25	0.25	Schell (2017)
C. tropicalis	**151**	**0.03 – 0.5**	**0.06 – 0.25**	**0.25 - 1**	**ALL STUDIES**
	50		0.06	0.5	PD002
	12	0.03 – 0.5	0.12	0.25	SCY078-MB-003
	31	0.06 – 2	0.25	0.5	SCY078-MB-006
	10	0.125 – 0.5	--	0.5	SCY078-MB-021
	21	0.06 – 2	0.25	1	Pfaller (2013)
	15	0.06 – 0.25	0.12	--	Jimenez-Ortigosa (2014)
	12	0.03 – 0.5	0.25	0.25	Schell (2017)
C. lusitaniae	**43**	**0.5 - >4**	**2**	**4 - >4**	**ALL STUDIES**
	5	0.5 – 4			PD002
	3	1 – 2	--	--	SCY078-MB-003
	10	0.5 - >4	2	>4	SCY078-MB-015
	22	0.5 – 4	2	4	SCY078-MB-006
	3	1 – 2	--	--	Schell (2017)
C. guillermondii	**41**	**1 – 4**	**1 – 2**	**1 – 4**	**ALL STUDIES**
	18		1	1	PD002
	23	1 – 4	2	4	SCY078-MB-006
C. dubliniensis	**26**	**0.06 – 0.25**	**0.12**	**0.25**	**ALL STUDIES**
	5	0.12	--	--	SCY078-MB-003
	20	0.06 – 0.25	0.12	0.25	SCY078-MB-006
	1	0.12	--	--	Jimenez-Ortigosa (2014)
C. auris	**433**	**0.06 – 8**	**0.5 – 1**	**0.5 – 1**	**ALL STUDIES**
	16	0.5 – 1	1	1	SCY078-MB-013
	100	0.06 – 2	0.5	1	Berkow (2017)
	195	0.06 – 8	0.5	0.5	Zhu (2020)
	122	0.06 – 2	--	--	Arendrup (2020)
C. orthopsilosis	**25**	**0.06 – 1**	**0.5**	**0.5 – 1**	**ALL STUDIES**
	15	0.06 – 1	0.5	0.5	SCY078-MB-006
	10	0.125 – 1		1	SCY078-MB-021
C. pediculosa	**15**	**0.25 – 2**	**0.25**	**2**	**SCY078-MB-006**
C. keyfr	12	0.06 – 1	0.5	1	SCY078-MB-006

Ibrexafungerp in vitro activity against known *fks1* or *fks2* mutations commonly associated with echinocandin resistance, phenotypic resistance, or clinical resistance ranged from 0.06 – 4 µg/mL, depending on the isolate (**Table 16-2**). Studies showed that modifications in position 641 of the *fks1* HS1 region in *C. albicans* isolates or position 655 in *fks1* for *C. krusei* or position 625 for *C. glabrata* and position F659 in *fks2* had greater impacts on ibrexafungerp MICs compared to echinocandins (Pfaller [2013]; Marcos-Zambrano [2017]).

Table 16-2. Activity of ibrexafungerp against echinocandin resistant Candida isolates

Organisms	N	Range	MIC50	MIC90	Reference
C. albicans	**22**	**≤0.03 – 1**	**0.5 – 1**	**2**	**ALL STUDIES**
	12	0.12 – 2	0.5	2	Pfaller (2013)
	10	≤0.03 – 1	1	--	Jimenez-Ortigosa (2014)
C. glabrata	**23**	**0.25 – 8**	**0.5 - 1**	**2**	**ALL STUDIES**
	12	0.5 – 2	1	2	Pfaller (2013)

Organisms	N	Range	MIC50	MIC90	Reference
	11	0.25 – 8	0.5	--	Jimenez – Ortigosa (2014)
C. krusei	**6**	**0.25 – 2**	**--**	**--**	**ALL STUDIES**
	2	0.5 – 2	--	--	Pfaller (2013)
	4	0.25 – 2	--	--	Jimenez-Ortigosa (2014)
C. tropicalis	**9**	**0.25 – 4**	**--**	**--**	**ALL STUDIES**
	5	0.25 – 2	--	--	Pfaller (2013)
	4	0.25 – 4	--	--	Jimenez-Ortigosa (2014)
C. dubliniensis	**1**	**0.12**	**--**	**--**	**Jimenez-Ortigosa**

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

16.4.1. Bioanalytical Methods

Review of the bioanalytical methods utilized to quantify plasma and urine ibrexafungerp concentrations in the clinical pharmacology studies are summarized in Table 16-3 and Table 16-4, respectively.

Table 16-3. Validation Reports of Quantification of Ibrexafungerp in Plasma

Bioanalytical method validation report: (b) (4)-962		
Studies analyzed by this method	SCY-078-001, SCY-078-002, SCY-078-003, SCY-078-008, SCY-078-014	
Analyte/assessment	Ibrexafungerp	
Method	HPLC-MS/MS	
Matrix	EDTA K2Plasma	
Validation Report	Validation reports provided:	☒ Yes ☐ No
	Validation report acceptable: Range: 1-2500 ng/mL	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period:	☒ Yes ☐ No
	Quality control (QC) samples range acceptable: QC: 2.5, 400, and 2000 ng/mL	☒ Yes ☐ No
	Chromatograms provided:	☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable:	☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable:	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable:	☒ Yes ☐ No
	Overall performance reasonable:	☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected?	☐ Yes ☒ No
Stability	Freeze-thaw and bench-top stability acceptable:	☒ Yes ☐ No
Bioanalytical method validation report (b) (4)-962A		
Studies analyzed by this method	SCY-078-015 and SCY-078-016	
Analyte/assessment	Ibrexafungerp	
Method	HPLC-MS/MS *Note: This method is a modification of (b) (4) 962 and includes a change in the concentration range from 1-2500 ng/mL to 5-2500 ng/mL and in increase in the sample reconstitution volume from 250 to 300 µL.*	
Matrix	EDTA K2Plasma	
Validation Report	Validation reports provided:	☒ Yes ☐ No

	Note: A partial validation study was completed to evaluate selected performance characteristics (selectivity, sensitivity, precision and accuracy) of the modified method.
	Validation report acceptable: ☒ Yes ☐ No Range: 5 to 2,500 ng/mL
Performance Report	Samples analyzed within the established stability period: ☒ Yes ☐ No
	Quality control (QC) samples range acceptable: ☒ Yes ☐ No QC: 5, 15, 400, and 2000 ng/mL
	Chromatograms provided: ☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable: ☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable: ☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable: ☒ Yes ☐ No
	Overall performance reasonable: ☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected? ☐ Yes ☒ No
Stability	Freeze-thaw and bench-top stability acceptable: ☒ Yes ☐ No
Bioanalytical method validation report: (b) (4) 001	
Studies analyzed by this method	SCY-078-102, SCY-078-103, SCY-078-104, SCY-078-107, SCY-078-111
Analyte/assessment	Ibrexafungerp
Method	LC-MS/MS
Matrix	EDTA K2Plasma
Validation Report	Validation reports provided: ☒ Yes ☐ No *Note: (b) (4) provided a full validated report for SCYNEXIS-sponsored studies. This method was later transferred to both (b) (4) where acceptable partial validation reports were submitted to verify satisfactory performance at each facility.*
	Validation report acceptable: ☒ Yes ☐ No Range: 5 to 5,000 ng/mL
Performance Report	Samples analyzed within the established stability period: ☒ Yes ☐ No
	Quality control (QC) samples range acceptable: ☒ Yes ☐ No QC: 5, 15, 150, and 4,000 ng/mL
	Chromatograms provided: ☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable: ☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable: ☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable: ☒ Yes ☐ No
	Overall performance reasonable: ☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected? ☒ Yes ☐ No
Stability	Freeze-thaw and bench-top stability acceptable: ☒ Yes ☐ No
Bioanalytical method validation report: (b) (4) -385	
Studies analyzed by this method	SCY-078-108, SCY-078-115
Analyte/assessment	Ibrexafungerp
Method	LC-MS/MS
Matrix	EDTA K2Plasma
Validation Report	Validation reports provided: ☒ Yes ☐ No *Note: This method is a modification of (b) (4) L001 and includes an adjustment of the final dilution step from 9-fold to 4-fold to allow for injection on an API4000 instrument, with the injection volume also changed to 20 µL.*
	Validation report acceptable: ☒ Yes ☐ No

	Range: 5 to 5,000 ng/mL *Note: A partial validation study was completed to evaluate selected performance characteristics (selectivity, sensitivity, precision, accuracy and stability) of the modified method.*
Performance Report	Samples analyzed within the established stability period: ☒ Yes ☐ No
	Quality control (QC) samples range acceptable: ☒ Yes ☐ No QC: 5, 15, 375 and 3,750 ng/mL
	Chromatograms provided: ☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable: ☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable: ☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable: ☒ Yes ☐ No
	Overall performance reasonable: ☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected? ☒ Yes ☐ No
Stability	Freeze-thaw and bench-top stability acceptable: ☒ Yes ☐ No
Bioanalytical method validation report: (b) (4) 2817	
Studies analyzed by this method	SCY-078-116
Analyte/assessment	Ibrexafungerp
Method	LC-MS/MS
Matrix	EDTA K2Plasma
Validation Report	Validation reports provided: ☒ Yes ☐ No *Note: This method is a modification of (b) (4) 001 and includes an minor modifications to adapt the method to different equipment and operating environment.*
	Validation report acceptable: ☒ Yes ☐ No Range: 5 to 5,000 ng/mL *Note: A partial validation study was completed to evaluate selected performance characteristics (selectivity, sensitivity, precision and accuracy) of the modified method.*
Performance Report	Samples analyzed within the established stability period: ☒ Yes ☐ No
	Quality control (QC) samples range acceptable: ☒ Yes ☐ No QC: 5, 15, 150, and 4,000 ng/mL
	Chromatograms provided: ☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable: ☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable: ☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable: ☒ Yes ☐ No
	Overall performance reasonable: ☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected? ☒ Yes ☐ No
Stability	Freeze-thaw and bench-top stability acceptable: ☒ Yes ☐ No

Table 16-4. Validation Reports of Quantification of Ibrexafungerp in Urine

Bioanalytical method validation report: (b) (4) 002	
Studies analyzed by this method	SCY-078-111
Analyte/assessment	Ibrexafungerp
Method	LC-MS/MS
Matrix	Human urine containing 1% (v/v) of a 20% TPGS solution
Validation Report	Validation reports provided: ☒ Yes ☐ No
	Validation report acceptable: ☒ Yes ☐ No

	Range: 0.500 to 250 ng/mL	
Performance Report	Samples analyzed within the established stability period:	☒ Yes ☐ No
	Quality control (QC) samples range acceptable: QC: 1.5, 15, 200 ng/mL	☒ Yes ☐ No
	Chromatograms provided:	☒ Yes ☐ No
	Accuracy and precision of calibration curve acceptable:	☒ Yes ☐ No
	Accuracy and precision of QC samples acceptable:	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable:	☒ Yes ☐ No
	Overall performance reasonable:	☒ Yes ☐ No
Inspection	Was the bioanalytical site inspected?	☒ Yes ☐ No
Stability	Freeze-thaw and bench-top stability acceptable:	☒ Yes ☐ No

16.4.2. Individual Study Reviews

Human PK Studies in Healthy Volunteers

Single and Multiple Ascending Dose

Study SCY-078-001 was a single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics of ibrexafungerp in healthy male subjects in the fasted state and after a high-fat meal. Sixteen subjects were enrolled and randomized to receive ibrexafungerp (N= 6 active and N=2 placebo per panel) with a minimum of a 7-day washout between each dosing period and at least 3 days between each panel. Ibrexafungerp was supplied as 10 mg and 100 mg phosphate capsules.

- Panel A: Single oral doses of 10, 40, 150, 60 and 1600 mg or matching placebo were administered in the fasted state.
- Panel B: Single oral doses of 20, 80, 300 and 800 mg or matching placebo were administered in the fasted state; and 80 mg of ibrexafungerp or matching placebo were administered with a standard high-fat breakfast.

Samples were collected from various matrices for measurement of ibrexafungerp and possible metabolites

- Plasma: intensive collection up to 72 hours post-dose
- Gastrin: 24 hours post-dose in a fasting state

Reviewer Comment: Urine samples were planned to be obtained only in Panel A, Periods 4 and 5; however, there is no documentation of the disposition of urine samples and no urinary ibrexafungerp concentrations are available.

Ibrexafungerp AUC and Cmax increased in proportion to dose up to the maximum dose tested in this study (1600 mg fasted) with a median Tmax of 4 to 6 hours and a half-life of approximately 20 hours. There were no clear overall changes in gastrin levels from baseline (pre-dose) to 24 hours post-dose for the ibrexafungerp doses evaluated.

A modest food effect was observed. Administration of ibrexafungerp 80 mg in the fed state compared to administration of ibrexafungerp 80 mg in the fasted state resulted in a mild

increase in bioavailability of ibrexafungerp (AUC and Cmax increased by ~20%), based on the Fed/Fasted GMR (90% CI) results for AUC0-∞ of 1.28 (0.96, 1.70) and Cmax of 1.19 (0.86, 1.66).

Reviewer Comment: Food effect results from this study were not used in labeling since it did not evaluate the to be marketed citrate salt tablet formulation.

Table 16-5. Summary of Ibrexafungerp Pharmacokinetic Parameters Following Single Oral Doses of Ibrexafungerp (10 mg to 1600 mg)

Dose[a]	N	$AUC_{0-\infty}$ µM•hr	AUC_{0-24hr} µM•hr	C_{max} (nM)	T_{max} (hr)	$t_{1/2}$ (hr)
		Geometric Mean (90% CIs)[b]	Geometric Mean (90% CIs)[b]	Arithmetic Mean ± SD	Median (Min – Max)	Harmonic Mean ± Pseudo SD
10 mg	6	0.15 (0.12, 0.19)	0.08 (0.06, 0.10)	6.13 ± 0.98	4.0 (2.0 – 6.0)	21.0 ± 9.2
20 mg	6	0.26 (0.21, 0.33)	0.16 (0.13, 0.21)	12.75 ± 6.29	5.0 (2.0 – 6.0)	16.4 ± 2.7
40 mg	6	0.62 (0.50, 0.78)	0.38 (0.30, 0.47)	30.87 ± 11.99	5.0 (4.0 – 6.0)	17.8 ± 3.2
80 mg	6	1.33 (1.06, 1.66)	0.79 (0.64, 0.99)	60.24 ± 16.61	4.0 (2.0 – 6.0)	21.1 ± 1.9
80 mg Fed	6	1.70 (1.36, 2.12)	0.96 (0.77, 1.20)	71.93 ± 21.87	5.0 (4.0 – 6.0)	19.9 ± 1.6
150 mg	6	3.27 (2.62, 4.09)	1.95 (1.56, 2.43)	167.86 ± 45.31	6.0 (4.0 – 6.0)	19.7 ± 2.3
300 mg	6	7.13 (5.71, 8.91)	4.15 (3.33, 5.16)	349.15 ± 72.77	6.0 (4.0 – 6.0)	20.5 ± 2.0
600 mg	7	17.97 (14.62, 22.09)	10.83 (8.84, 13.26)	875.86 ± 261.63	6.0 (4.0 – 6.0)	18.7 ± 3.6
800 mg	6	20.07 (16.06, 25.09)	11.54 (9.26, 14.37)	895.60 ± 409.47	5.0 (4.0 – 6.0)	19.3 ± 1.6
1600 mg	5	51.60 (40.42, 65.87)	28.12 (22.11, 35.76)	2085.40 ± 754.71	6.0 (2.0 – 8.0)	20.9 ± 2.7

[a] All doses administered in fasted state except the 80 mg Fed group as noted above.
[b] AUCs are presented as geometric means with associated 90% CIs to address the protocol hypothesis.

Single oral doses of ibrexafungerp up to 1600 mg were generally safe and well tolerated in these healthy adult male subjects. The most common treatment-emergent related AEs involved the gastrointestinal system and were reported in 7 of 16 subjects (43.8%) in the higher dose cohorts of 600, 800 or 1600 mg, and no subjects who received doses ≤ 300 mg. There were no serious adverse events with the exception of one serious adverse event of abdominal pain following the 1600 mg dose.

Study SCY-078-002 was a multiple dose safety, tolerability, and PK study of oral Ibrexafungerp in 32 healthy adult male subjects, in which 24 received ibrexafungerp (N=6 per panel) and 8 received placebo (N=2 per panel). One subject in Panel E withdrew consent and discontinued after receiving 11 daily doses of ibrexafungerp 800 mg.

- Panel A - 300 mg×10 days

- Panel B - 600 mg×10 days
- Panel C - 800 mg×10 days
- Panel E - 800 mg×28 days

Intensive plasma samples were collected up to 72 hours post-dose on Day 10. Urine samples were collected in Part E at pre-dose on Day 1 at 4 intervals up to 24 hours on Day 26 post-dose. However, an exploratory assay revealed low concentrations insufficient for analysis.

Steady-state plasma concentrations of ibrexafungerp were achieved within approximately 2 weeks of daily dosing. AUC0-24 hr and Cmax, increased in an approximately dose proportional manner for the 300, 600, and 800 mg doses studied. Two-fold or higher accumulation for Cmax and AUC was observed at steady-state with repeated daily dosing of ibrexafungerp.

Table 16-6. Summary of Plasma Ibrexafungerp Pharmacokinetic Results

PK Parameter	Study Day	Ibrexafungerp Dose Groups			
		300 mg × 10 days	600 mg × 10 days	800 mg × 10 days	800 mg × 28 days
		n = 6	n = 6	n = 6	n = 5
$AUC_{0\text{-}24hr}$ [a] (μM•hr)	1	3.82 (2.88, 5.07)	9.38 (6.09, 14.46)	12.53 (8.10, 19.37)	13.75 (6.71, 28.17)
	10 or 26	9.01 (6.79, 11.96)	21.11 (13.70, 32.54)	26.38 (17.06, 40.79)	45.85 (22.37, 93.97)
	AR[b]	2.36 (1.70, 3.26)	2.25 (1.37, 3.70)	2.11 (1.28, 3.48)	3.34 (1.47, 7.56)
C_{max} [a] (nM)	1	308.6 (224.5, 424.2)	705.9 (485.2, 1027)	1024 (680.7, 1539)	1112 (597.7, 2068)
	10 or 26	553.7 (402.8, 761.1)	1272 (874.3, 1851)	1609 (1070, 2420)	2634 (1416, 4900)
	AR[b]	1.79 (1.24, 2.59)	1.80 (1.17, 2.77)	1.57 (0.98, 2.51)	2.37 (1.17, 4.81)
C_{trough} [a] (nM)	1	89.52 (65.56, 122.2)	247.4 (150.8, 405.7)	275.9 (172.5, 441.3)	325.3 (137.4, 769.8)
	10 or 26	253.9 (186.0, 346.7)	613.2 (373.8, 1006)	790.6 (494.3, 1265)	1468 (620.4, 3476)
	AR[b]	2.84 (1.98, 4.06)	2.48 (1.40, 4.38)	2.87 (1.67, 4.92)	4.51 (1.69, 12.06)
T_{max}[c] (hr)	1	4.0 (2.0 – 6.0)	6.0 (4.0 – 6.0)	6.0 (2.0 – 6.0)	6.0 (2.0 – 6.0)
	10 or 26	6.0 (4.0 – 6.0)	6.0 (4.0 – 8.0)	6.0 (6.0 – 6.0)	6.0 (4.0 – 6.0)
$t_{½}$[d] (hr)	1	13.3 (2.6)	14.6 (3.9)	11.3 (1.8)	14.3 (3.5)
	10 or 26	24.7 (2.8)	28.9 (6.7)	32.3 (11.5)	22.6 (10.4)

Source: SCY-078-002 Table 14.2.2.1
[a] LS geometric means and associated 90% confidence intervals based on a linear model.
[b] AR = Accumulation Ratio, GMR Last/Day 1 (Minimum – Maximum).
[c] Median (Minimum – Maximum).
[d] Harmonic Mean (Pseudo SD).

The most common treatment-emergent AEs involved gastrointestinal disorders, nervous system disorders, and laboratory or vital signs investigations. There appeared to be more GI AEs (i.e., diarrhea, abdominal pain, abdominal pain upper, nausea, vomiting, gastrointestinal sounds abnormal, and epigastric discomfort) at ibrexafungerp doses above 300 mg. There were no clear-cut differences in the frequency of individual AEs for the 600 mg and 800 mg×10 day

dose groups, but there was an apparent higher frequency of GI AEs reported in the 800 mg×28 day dose group relative to the other ibrexafungerp dose groups. In the 800 mg×28 day dose group, GI AEs were reported with a similar or greater frequency in the first 10 days of treatment compared to the last 18 days, and did not appear to be related to the longer 28-day treatment exposure. All treatment-related AEs were mild or moderate in severity with all but one of the moderate severity treatment-related TEAEs was reported in the 800 mg×28 day dose group.

Study SCY-078-111 was a multiple-dose PK, safety and tolerability study of ibrexafungerp in healthy male subjects. A total of 16 subjects were enrolled, 2 cohorts of 8 subjects each. Each cohort received both active treatment and placebo during the 2 dosing periods (Period 1 and Period 2) in a cross-over design, with the 7-day washout period in between periods.

Period 1:

- Cohort A – Ibrexafungerp
  - Day 1 and Day 2: 750 mg BID
  - Day 3 through Day 7: 750 mg QD
- Cohort B – Placebo

Period 2:

- Cohort A – Placebo
- Cohort B – Ibrexafungerp
  - Day 15 and Day 16: 750 mg BID
  - Day 17 through Day 21 (EOT): 750 mg QD

Plasma PK samples were collected from each subject in Period 1 up to 24 hours post the first dose. An additional blood sample was collected prior to dosing on Days 3, 4, 5, and 6. In Period 2, blood samples were collected up to 120 hours post dose. Urine PK samples for the determination of ibrexafungerp were collected after the first dose on Days 1 and 7 in each period at the following time intervals: 0 - 4 hours, 4 – 8 hours, 8 - 12 hours, 12 - 16 hours, and 16 - 24 hours.

Following multiple oral doses of 750 mg ibrexafungerp BID on Days 1 and 2 followed by 750 mg ibrexafungerp QD on Days 3 – 7, steady-state levels were achieved for plasma by Day 4. A summary of plasma and urine PK parameters on Day 1 and Day 7 is highlighted in Table 16-7.

Table 16-7. Summary of Plasma and Urine Ibrexafungerp Pharmacokinetics Following the Administration of Multiple Oral Doses of 750 mg Ibrexafungerp BID (Days 1 and 2) and 750 mg Ibrexafungerp QD (Days 3 - 7) – Day 1 and Day 7 (PK Population)

Matrix	Pharmacokinetic Parameters	SCY-078 BID; Day 1	SCY-078 QD; Day 7
Plasm	AUC0-12 (ng*hr/mL)	6283 (25.1) [n=16]	15630 (25.7) [n=16]
	AUC0-24 (ng*hr/mL)	16190 (25.1) [n=16]	.
	AUC0-tau (ng*hr/mL)	.	28160 (28.3) [n=16]
	AUC0-last (ng*hr/mL)	.	68210 (40.2) [n=16]
	AUC0-inf (ng*hr/mL)	.	78250 (45.5) [n=16]
	Cmax (ng/mL)	724.1 (23.4) [n=16]	.
	Cmax,ss (ng/mL)	.	1497 (23.9) [n=16]
	Cmin,ss (ng/mL)	.	889.6 (35.2) [n=16]
	Cavg (ng/mL)	.	1173 (28.3) [n=16]
	Tmax (hr)	6.001 (4.01, 11.92) [n=16]	.
	Tmax,ss (hr)	.	6.000 (4.04, 6.03) [n=16]
	Tmin,ss (hr)	.	24.000 (2.00, 24.02) [n=16]
	t½ (hr)	.	41.071 ± 9.4068 [n=16]
	RA,Cmax	.	2.11 ± 0.400 [n=16]
	RA,AUC	.	2.54 ± 0.524 [n=16]
Urine	Ae,cum (mg)	0.4877 (49.9) [n=15]	0.6051 (58.7) [n=16]
	Cmax,u (ng/mL)	386.62 (74.0) [n=16]	513.39 (54.1) [n=16]
	Cmin,u (ng/mL)	46.77 (89.4) [n=16]	172.92 (158.6) [n=16]
	Cavg,u (ng/mL)	210.15 (57.6) [n=16]	325.71 (44.7) [n=16]
	CLr (mL/h)	30.57 (43.7) [n=15]	22.13 (41.2) [n=16]

SCY-078: Multiple oral doses of 750 mg SCY-078 BID (Days 1 and 2) and 750 mg SCY-078 QD (Days 3 - 7).
. = Value missing or not reportable
AUCs, Cmax, Ae,cum, Cmax,u, Cmin,u, and Cavg,u values are presented as geometric mean and geometric CV%.
Tmax, Tmax,ss, and Tmin,ss values are presented as median (min, max).
Other parameters are presented as arithmetic mean (± SD).
Source: Tables 14.2.1.3 through 14.2.1.4, Tables 14.2.3.1 through 14.2.3.2
Program: /CA24703/sas_prg/pksas/adam_intext_pkparam.sas 28NOV2018 13:08

The most common adverse events were diarrhea (n=7 or 44% of subjects), abdominal pain (n=3 times or 19% of subjects) and headache (n=3 or 19% of subjects), all of which were related to the study drug apart from one subject who experienced headache after placebo.

Study SCY-078-014 was a multiple dose safety, tolerability, and PK study of oral ibrexafungerp in 8 healthy male subjects (N=6 active drug and N=2 placebo).

- Day 1: 1800 mg loading dose administered as 600 mg three times daily (TID)
- Days 2 through 7: followed by 500 mg ibrexafungerp once daily (QD)

Blood samples for plasma PK were collected up 24 hours post-dose on Days 1 and 3 and up to 96 hours post-dose on Day 7. Trough PK samples were collected on Days 2 through 7.

A summary of ibrexafungerp PK parameters by visit (Days 1, 3 and 7) is shown in Table 16-8.

Table 16-8. Summary of Plasma Ibrexafungerp Pharmacokinetic Results

Visit	N	$AUC_{0\text{-}24hr}$ (µM•hr)[a]	C_{max} (nM)[a]	T_{max} (hr)[b]	$t_{1/2}$ (hr)[c]
Day 3/Day 1					
Day 1	6	20.75 (15.85, 27.18)	1542 (1159, 2052)	6.0 (4.0 – 6.0)	
Day 3	6	20.95 (16.00, 27.44)	1196 (899 1591)	6.0 (6.0 – 6.0)	19.3 ± 7.0
GMR[d]		1.01 (0.74, 1.38)	0.78 (0.56, 1.08)		
Day 7/Day 1					
Day 1	6	20.75 (15.85, 27.18)	1542 (1159, 2052)	6.0 (4.0 – 6.0)	
Day 7	6	16.11 (11.49, 22.58)	959 (694, 1325)	5.0 (2.0 – 6.0)	25.6 ± 5.3
GMR[d]		0.78 (0.53, 1.14)	0.62 (0.43, 0.90)		

Source: Table 14.2.2.1 and Data Listing 16.2.6.1
[a] LS Geometric Mean and its 95% CI were calculated based on linear model: log (PK Result) =visit.
[b] Median (Min – Max)
[c] Harmonic Mean ± Pseudo SD
[d] Geometric Mean Ratio, GMR Day X/Day 1 (90% CI)

Three subjects receiving ibrexafungerp reported four AEs of diarrhea possibly related to study drug. Three of the episodes of diarrhea occurred on Day 1 after the first or second dose of 600 mg, and one episode occurred on Day 2 after the 500-mg dose. All episodes of diarrhea resolved within 1 day, and there were no additional episodes of diarrhea with repeated daily ibrexafungerp doses. No other AEs were reported during the study.

Study SCY-078-003 was a single dose study to evaluate the safety, tolerability, and pharmacokinetics of Ibrexafungerp in elderly subjects. A single 500-mg oral doses of ibrexafungerp (n=13) or placebo (n=4) was administered to healthy elderly men (Panel A) and women (Panel B) during a single treatment period. In each Panel, 6 subjects received ibrexafungerp and 2 subjects received placebo. Pharmacokinetics in the elderly were compared to the Cohort of Young Men from Study 001, who received the 500 mg single dose. All doses were administered as phosphate salt 100 mg capsules.

Plasma samples were obtained for measurement of ibrexafungerp concentration predose and up to 96 hours post-dose.

Twelve subjects were included in the PK analysis (Table 16-9). The elderly males had a mean age (SD) of 68.9 (3.13) with a range of 65 to 75 years. The elderly females had a mean age (SD) of 68.3 (3.78) with a range of 66 to 76 years. Data for young male subjects were obtained from historical data (SCY-078-001, dose range 10 to 1600 mg). Since the pharmacokinetic parameters were dose proportional over the dose range studied in SCY-078-001, the historical healthy young male data were dose-adjusted to 500 mg then averaged by subject. The mean (SD) age of

subjects receiving ibrexafungerp in Study SCY-078-001 (all doses pooled) was 27.9 (7.81%) years (range: 20 to 45 years).

The results indicated that PK exposures in the elderly subjects were approximately 1.4-fold above young subjects, AUC∞ GMR (90% CI) was 1.38 (1.19, 1.62).

Table 16-9. Summary of Between-Population Comparisons (Elderly Subgroups in Protocol 003 and Healthy Young Males in Protocol 001) for Ibrexafungerp AUC0-∞, Cmax, and AUC0-24hr – Per Protocol Population

Pharmacokinetic Parameters	LS GMR[a] (90% CI)	
	Elderly Females vs. Elderly Males	Pooled Elderly vs. Young Males[b]
$AUC_{0-\infty}$ (nM•hr)	1.08 (0.81, 1.44)	1.39 (1.19, 1.62)
C_{max} (nM)	1.09 (0.82, 1.46)	1.29 (1.10, 1.50)
AUC_{0-24hr} (nM•hr)	1.10 (0.85, 1.42)	1.23 (1.06, 1.42)

Source: SCY-078-003 Table 14.2.2.1.1, Table 14.2.2.1.2, and Data Listing 16.2.6.3
$AUC_{0-\infty}$ = area under the plasma concentration time curve from time 0 to infinity; AUC_{0-24hr} = area under the plasma concentration curve from time 0 to 24 hours postdose; C_{max} = maximum concentration of drug in the plasma; CI = confidence interval; GMR = geometric mean ratio; LS = least-squares.
[a] LS Geometric Mean and its 95% CI were calculated based on linear model: log (PK Result) = analysis visit. Geometric Mean Ratios: Elderly Female / Elderly Male (90% CI) and Pooled Elderly / Young Male (90% CI).
[b] Data for young male subjects were obtained from historical data (SCY-078-001, dose range 10 to 1600 mg). Since the pharmacokinetic parameters were dose proportional over the dose range studied in SCY-078-001, the historical healthy young male data were dose-adjusted to 500 mg then averaged by subject.

The most common treatment-emergent AEs were diarrhea (n=4 or 30% of subjects) and headache (n=3 or 23% of subjects).

Reviewer Comment: Age was also assessed in the population PK model where age was a predictor of peripheral volume. The difference in exposures related to age is ≤5% in Cmax or AUC0-24 and is not a clinically relevant covariate with respect to the magnitude of effect. Dose adjustment for age is not required.

Mass Balance

Study SCY-078-116 evaluated the mass balance of ibrexafungerp in 6 healthy subjects exposed to a single dose of 300 mg free-base of [14C]-ibrexafungerp (96 micro Ci). Matrices collected included blood (intensive sampling for whole blood and plasma concentrations up to 168 hours post dose), urine (intervals of six or 24 hours up to 216 hours post dose) and feces (24-hour intervals up to 384 hours post dose).

The blood-to-plasma ratios of total radioactivity at all PK time points assessed were less than 1, indicating preferential distribution of total radioactivity to the plasma. The total mean recovery (urine + feces) was approximately 89.56% (N=4).

The majority of total radioactivity (an average of 88.36% of the dose administered, over 98% of the dose recovered) was recovered in the feces, indicating fecal excretion was the main route of elimination, with an average of 1.20% (minimum, 0.54%; maximum, 1.68%) recovered in urine.

Table 16-10. Mean Cumulative Amount Excreted of Total Radioactivity in Urine, Feces and Urine and Feces Combined Following a Single Oral Dose of [14C]-Ibrexafungerp to Healthy Male Subjects

Collection Interval[a] (h)	Cumulative Urine Ae (%)	Cumulative Faeces Ae (%)	Cumulative Total Ae (%)
0 – 24	0.59	3.28	3.87
0 – 48	0.83	19.63	20.47
0 – 72	0.97	38.92	39.89
0 – 96	1.06	54.16	55.22
0 – 120	1.11	62.28	63.39
0 – 144	1.15	77.32	78.47
0 – 168	1.18	83.18	84.36
0 – 192	1.19	84.68	85.87
0 – 216	1.20	86.34	87.55
0 – 240	1.20	86.80	88.00
0 – 264	1.20	87.00	88.21
0 – 288	1.20	87.54	88.74
0 – 312	1.20	87.94	89.14
0 – 336	1.20	88.14	89.34
0 – 360	1.20	88.33	89.54
0 – 384	1.20	88.36	89.56
Ae(total) (mg equiv)	3.50	257	261

[a] Urine samples collected to 216 h only, values carried forward.

Exposure to ibrexafungerp accounted for 32% of circulating plasma total radioactivity based on AUC0-last, indicating that there are additional circulating components in plasma following administration of [14C]-ibrexafungerp. The geometric mean observed terminal half-life of total radioactivity in plasma and whole blood (45.906 hours and 43.836 hours, respectively) were both longer than that observed for ibrexafungerp (27.947 h), suggesting the presence of uncharacterized metabolite(s) with longer terminal elimination half-lives.

Reviewer Comment: Only 19.63% of total radioactivity was recovered in feces within the first 2 days of dosing indicating that the majority of fecal recovery was a result of biliary elimination, rather than excretion of unabsorbed drug.

Plasma and fecal pooled samples from this study were subsequently evaluated for metabolite profiling. The only major peak in plasma samples identified belonged to the parent ibrexafungerp that was about 38% of total radioactivity in the plasma. No metabolites

were found that were over 10% of total radioactivity in the plasma. The major peak in feces samples identified was ibrexafungerp, which accounted for 51% of administered dose. The sulfate metabolite of mono-hydroxy ibrexafungerp accounted for 13% of administered dose with all other metabolites <10% of administered dose.

Summary of In Vitro Pharmacokinetics

Absorption

Ibrexafungerp was evaluated in Caco-2 cell monolayers in Study SCY078-ADME-14 and LLC-PK1 cells expressing the human (LLC-MDR1) or mouse (LLC-Mdr1a) P-glycoprotein (P-gp) in Study PK002. At 5 µM, ibrexafungerp was shown to be a substrate for P-gp in both studies. Ibrexafungerp showed permeability value of 5.2 to 11.7×10^{-6} cm/sec in Caco-2 cells at all concentrations (0.5 to 20 µM) tested.

Distribution

Study PK002 evaluated the blood-to-plasma partitioning of ibrexafungerp in DBA mouse, Sprague Dawley rat, Beagle dog, and rhesus monkey plasma and blood. [3H]-Ibrexafungerp at concentrations of 0.1, 1, and 10 µM were incubated with plasma and blood for 1 hr at 37°C. The blood-to-plasma partitioning ratio was 0.5 to 0.6 in all species over the concentration range tested.

In vivo studies also confirmed a blood-to-plasma ratio of <1.0 indicative of low red blood cell partitioning. In Study SCY078-ADME-001, the blood-to-plasma partitioning of ibrexafungerp in Sprague Dawley rats ranged from 0.71 at 30 min post-dose to 0.95 at 120 hr post-dose following oral administration of [3H]-ibrexafungerp at 5.04 mg/kg. In Study SCY078-ADME-037, the mean blood-to-plasma ratios for all doses ranged from 0.596 to 0.863 through 48 hr post-dose in Beagle dogs following oral administration of [14C]-ibrexafungerp at 5 mg/kg.

The extent of ibrexafungerp binding to human plasma proteins was determined in Study SCY078-ADME-055 using equilibrium dialysis at concentrations of 0.1 to 10 µg/mL. Very high levels of binding were observed, with bound (unbound) fractions of 99.8 (0.210), 99.8 (0.247), 99.8 (0.187), 99.6 (0.410), and 99.6 (0.397)%, respectively, at 0.1, 0.5, 1, 5, and 10 ng/mL, respectively.

Distribution into Vaginal Tissues and Vaginal Secretions

In Study SCY078-ADME-035, the PK and distribution of ibrexafungerp citrate to the kidneys, pulmonary fluid, and vaginal tissue was evaluated following single and repeat oral administration in female CD-1 mice. Whole blood, kidney tissue, vaginal lavage fluid, vulvovaginal tissue, and bronchoalveolar lavage fluid (BALF) samples were collected at pre-dose and up to 24 hr post final dose for each group. Ibrexafungerp accumulation in vaginal secretions was significant at all dose levels and increased in a dose-dependent manner (Table 16-11).

Table 16-11. Ibrexafungerp Exposure in Plasma, Vaginal Secretions, and Vaginal Tissue

Dose[a] (mg/kg)	Day[b]	Plasma		Vaginal Lavage Fluid/VS		Vaginal Tissue	
		C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)	C_{max} (µg/mL)	AUC_{0-24} (µg·h/mL)
10/5	1	0.738	7.47	0.00504	0.0716	1.87	24.6
	4	0.417	5.12	0.0197	0.200	1.92	24.4
20/10	1	1.40	16.6	0.0138	0.195	5.55	72.9
	4	1.22	14.6	0.0388	0.400	4.78	71.6
40/20	1	3.29	46.5	0.0344	0.490	10.7	204
	4	3.45	53.0	0.148	1.80	21.0	275
80/40	1	6.05	101	0.0705	0.824	19.7	337
	4	8.21	143	0.501	5.54	108	1798

AUC_{0-24}=area under the concentration versus time curve from time zero to 24 hr post-dose; BID=twice daily; C_{max}=mean maximum plasma concentration; VS=vaginal secretions

a. Doses were administered BID and are shown as loading/maintenance dose.

b. Exposures following the second daily dose are shown.

In a single dose study conducted in rats (SCY078-ADME-036), following oral administration of [14C]-Ibrexafungerp, the tissue-to-blood AUC ratio in vaginal tissue was 9X, indicating extensive distribution to vaginal tissues.

With repeat-dosing, ibrexafungerp has been shown to accumulate in vaginal tissue reaching exposures 5- to 10-fold higher than in plasma. Ibrexafungerp is fungicidal against *Candida* species and maintains in vitro activity at neutral and low pH (Study SCY078-MB-016).

Metabolism

The metabolic stability of ibrexafungerp was evaluated in human liver microsomes at 10 µM radiolabeled ([3H]) compound (Study PK002) and in human hepatocytes at 1 µM (Study SCY078-ADME-013). Extensive hydroxylation was noted for human liver microsomes. Ibrexafungerp was considered stable (t1/2>120 minutes) in human hepatocytes. The intrinsic clearance rate of ibrexafungerp at 1 µM was moderate in human hepatocytes (4 µL/min/106 cells, respectively).

Study SCY078-ADME-015 evaluated the in vitro stability of ibrexafungerp in human plasma and whole blood in (0.25 and 1 µM and 0.5 and 2 µM, respectively) and maintained at 0°C, 4°C, and ambient temperature (20 to 25°C) for up to 480 min. In whole blood, due to variable recovery of ibrexafungerp, results were not reportable; however, in plasma, percent remaining at 480 min ranged from 105 to 113% at all temperatures.

Study SCY078-ADME-017 evaluated the in vitro stability of ibrexafungerp in human and simulated gastric fluid samples (10 µM for 60 minutes). In human gastric fluid 100% and 96% ibrexafungerp remained, respectively, after 60 min (t1/2>180 min).

The metabolic profile of [3H]-ibrexafungerp (10 µM) in human liver microsomes (37°C for up to 1 hr) and in human hepatocytes (37°C for up to 2 hr) was evaluated in Study PK002. Extensive hydroxylation was noted in human liver microsomes. Parent glucuronidation was detected in human hepatocytes, along with sulfation of a hydroxylated metabolite. This metabolite represented <10% of the total radioactivity in human microsomes.

In Study SCY078-ADME-007, ibrexafungerp (10 µM) was incubated with human hepatic and intestinal microsomes to qualitatively compare metabolic profiles. Comparisons of mass shifts and chromatographic retention times for intestinal metabolites were consistent with metabolites produced by hepatic microsomes, thereby suggesting an absence of any major route-specific metabolites.

CYP450 Reaction Phenotyping

In vitro studies were conducted with human liver microsomes with selective chemical inhibitors (Study SCY078-ADME-013; Table 16-12) and recombinant CYP enzymes (Study SCY078-ADME-013; Table 18-13). Based on substrate depletion and oxidative metabolites formation in human liver microsomes and recombinant human CYP enzymes, cytochrome P450 CYP3A4 was shown to be primarily responsible for the in vitro intrinsic clearance of ibrexafungerp, with CYP3A5 appearing to contribute to a lower extent.

Table 16-12. Intrinsic Clearance and Oxidative Metabolite Formation of Ibrexafungerp in Human Liver Microsomes

Study	**SCY078-ADME-013**			
Dose	1 µM			
Analyte	Ibrexafungerp			
Test system	Human liver microsomes			
CYPs / Inhibitors	**Intrinsic Clearance (µL/min/mg)**	**Intrinsic Clearance (%)**	**Sum of oxidative metabolites[c]**	**Oxidative Metabolites (%)**
(-) Inhibitor	38	100%	0.307	100%
CYP3A / Ketoconazole (1 µM)	6.4	17%	0.013	4.1%
CYP2D6 / Quinidine (10 µM)	29	77%	0.260	85%
CYP2C19 / TCP (50 µM)	30	80%	0.304	99%
CYP2C9 / Sulfaphenazole (10 µM)	37	99%	0.299	98%
CYP2A6 / TCP (10 µM)	36	95%	0.316	103%
CYP2C8 / Quercetin (20 µM)	23	61%	0.263	86%
CYP2E1 / DDTC[a] (100 µM)	31	82%	0.220	72%
(-) Inhibitor[b]	32	100%	0.307	-
CYP2B6 / Ticlopidine (5 µM)[b]	28	89%	0.305	99%

CYP=cytochrome P450; DDTC=diethyldithiocarbamate; NADPH=nicotinamide adenine dinucleotide phosphate; TCP=tranylcypromine
Diethyldithiocarbamate
Incubation was performed on a different date from the other incubations.
Sum of peak area ratios of 5 different oxidative metabolites, except for 3 different metabolites for CYP2B6, monitored in the samples at 45 minutes.
Note: µM substrate in 0.5 mg/mL of microsomal protein in the presence of NADPH (1 mM).

Table 16-13. Intrinsic Clearance and Oxidative Metabolite Formation of Ibrexafungerp in Recombinant Human P450s

Study		SCY078-ADME-013		
Dose		1 µM		
Analyte		Ibrexafungerp		
Test system		Recombinant human CYP enzymes		
Recombinant Human (rh) P450s	NADPH	% Remaining at 30 Minutes	Half-life ($t_{1/2}$, min)	Intrinsic Clearance (µL/min/pmol of P450)
rhCYP3A4	(+)	24%	16	0.86
rhCYP3A5	(+)	68%	57	0.24
rhCYP2B6	(+)	80%	95	0.15
rhCYP1A2	(+)	83%	131	0.11
rhCYP vector	(+)	78%	88	0.16
rhCYP3A4	(-)	87%	101	0.14
rhCYP3A5	(-)	85%	>135	<0.1
rhCYP2B6	(-)	78%	101	0.14
rhCYP1A2	(-)	90%	>135	<0.1
rhCYP vector	(-)	74%	80	0.17

CYP=cytochrome P450; min=minute; NADPH=nicotinamide adenine dinucleotide phosphate; rhCYP=recombinant human CYP; $t_{1/2}$=half-life
Note: 1 µM substrate in 50 pmol/mL of rhCYP enzymes in the absence or presence of NADPH
Note: Incubations were performed for 1 hour at 37°C with ibrexafungerp at 10 µM.

To determine the metabolism and potential Km and Vmax of ibrexafungerp in human hepatic microsomes, ibrexafungerp (1 to 80 µM) was incubated at 37°C for up to 1 hr in the presence and absence of NADPH (Study SCY078-ADME-060). Samples were assayed by LCMS/ MS and kinetic parameters determined for the disappearance of ibrexafungerp. Overall, the metabolism of ibrexafungerp followed Michaelis-Menten kinetics with an apparent Km value of 15.5 µM and Vmax of 363 pmol/min/mg.

UGT Reaction Phenotyping

In vitro metabolic stability of ibrexafungerp was evaluated in the absence or presence of borneol, an inhibitor of glucuronidation, in human hepatocytes (Study SCY078-ADME-030;Table 16-14). Ibrexafungerp glucuronide was formed only following incubation of ibrexafungerp with rhUGT1A3 and human liver microsomes, suggesting that UGT1A3 is responsible for ibrexafungerp glucuronidation among UGT enzymes studied.

Table 16-14. UGT Reaction Phenotyping

Study	SCY078-ADME-030					
Dose	1 µM					
Analyte	Ibrexafungerp					
Test system	Human recombinant UGT (rhUGT) enzymes and human liver microsomes (HLM)					
Recombinant Human (rh) UGTs	**0 min**	**5 min**	**10 min**	**20 min**	**30 min**	**45 min**
rhUGT1A1	0	0	0	0	0	0
rhUGT1A3	0.000	0.003	0.005	0.010	0.013	0.020
rhUGT1A4	0	0	0	0	0	0
rhUGT1A6	0	0	0	0	0	0
rhUGT1A9	0	0	0	0	0	0
rhUGT2B7	0	0	0	0	0	0
rhUGT vector	0	0	0	0	0	0
HLM	0.000	0.006	0.012	0.026	0.034	0.048
Recombinant Human (rh) UGTs	**0 min**	**10 min**	**20 min**	**30 min**	**45 min**	**60 min**
rhUGT1A3	0.000	0.009	0.020	0.026	0.041	0.052
rhUGT1A8	0	0	0	0	0	0
rhUGT1A10	0	0	0	0	0	0
rhUGT2B17	0	0	0	0	0	0
rhUGT vector	0	0	0	0	0	0
HLM	0.000	0.020	0.039	0.055	0.079	0.106

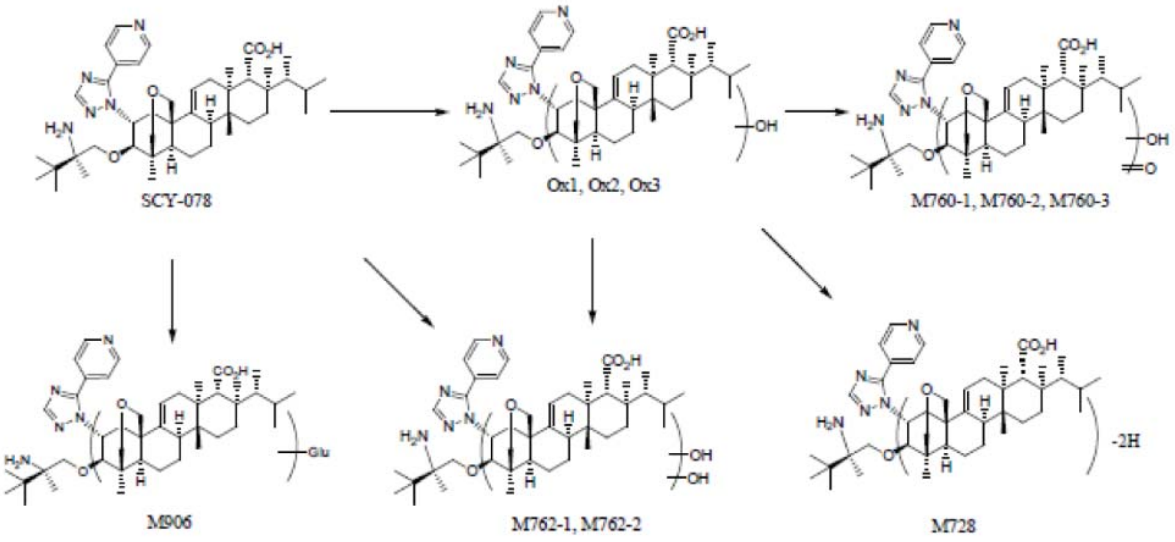
HLM=human liver microsomes; rhUGT=recombinant human UGT; UDPGA=uridine 5'-diphosphoglucuronic acid; UGT=uridine 5'-diphospho-glucuronosyltransferase
Note: 1 µM substrate in 0.5 mg/mL of rhUGT enzymes or 0.5 mg/mL of HLM in the presence of UDPGA

In Vitro Metabolism

In Study SCY-ADME-041, semi-quantitative analysis of ibrexafungerp and metabolites was performed using LC-MS/MS to profile and identify metabolites of ibrexafungerp in human plasma samples from Study SCY-078-103. Plasma samples were collected on Day 1 up to 24 hours post-dose from two subjects.

Parent ibrexafungerp and M906 (glucuronidation) were detected as major drug related components. In addition, Ox1 (M746-1, oxidation), Ox2 (M746-2, oxidation), Ox3 (M746-3, oxidation), M760-1, M760-2, M760-3 (di-oxidation dehydrogenation), M762-1, M762-2 (dioxidation), and M728 (dehydrogenation) were also observed (Figure 3).

Figure 3. Proposed Biotransformation Products of Ibrexafungerp in Humans



Reviewer Comment: In the exploratory non-clinical metabolism study SCY078-MB-012, the Applicant identified two minor putative metabolic components (<5%; SCY-PYR and SCY-TBU) that had antifungal activity against Candida spp. comparable (within 2-fold dilution) to that of ibrexafungerp (MIC50 values of 0.5, 0.5, and 0.25 µg/mL, respectively. It should be noted that neither compound was observed as a metabolite in the nonclinical (rat or dog) or human 14C radiolabel studies. Further, results from the human mass balance study showed that all circulating plasma metabolites were less than 10% and therefore were not identified. These two metabolites have no clinical relevance.

In Vitro Drug-Drug Interaction Studies

Study PK002 evaluated the reversible inhibitory effects of ibrexafungerp on pooled human liver microsomal activity for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The probe substrates (and metabolites) used are outlined in Table 16-15.

Ibrexafungerp was a potent reversible inhibitor of CYP2C8 (IC50 of 1.5 µM) and a moderate inhibitor of CYP3A4 (IC50 of 7.2 µM); however, ibrexafungerp was not shown to inhibit the other CYP isoforms to any appreciable degree. Ibrexafungerp was not a time-dependent inhibitor of CYP3A4 at 10 µM or 50 µM.

Table 16-15. Effect of Ibrexafungerp on Cytochrome P450 Activity in Pooled Human Liver Microsomes (Reversible Inhibition)

CYP	Reaction	Study: PK002	
		Absolute IC_{50} (µM)[a], Relative IC_{50} (µM)[b]	
		Control Inhibitor	Ibrexafungerp
1A2	Phenacetin O-Deethylation	0.0083, 0.0066 ± 0.00039 (α-Naphthoflavone)	>100, >100 (22 ± 1.3%)[c]
2B6	Bupropion Hydroxylation	0.72, 0.67 ± 0.048 (Ticlopidine)	26, 25 ± 1.6
2C8	Amodiaquine N-Deethylation	0.15, 0.16 ± 0.0095 (Montelukast)	1.5, 1.5 ± 0.088
2C9	Diclofenac 4'-Hydroxylation	0.82, 0.81 ± 0.045 (Sulfaphenazole)	60, 60 ± 2.5
2C19	S-Mephenytoin 4'-Hydroxylation	0.20, 0.20 ± 0.0039 (Benzylnirvanol)	>100, >100 (32 ± 0.74%)
2D6	Dextromethorphan O-Demethylation	0.091, 0.084 ± 0.0062 (Quinidine)	41, 42 ± 0.91
3A4	Midazolam 1'-Hydroxylation	0.029, 0.027 ± 0.0014 (Ketoconazole)	7.2, 6.8 ± 0.19
3A4	Testosterone 6β-Hydroxylation	0.028, 0.028 ± 0.0013 (Ketoconazole)	15, 15 ± 0.44

CYP=cytochrome P450; IC_{50}=median inhibitory concentration
a. The absolute IC_{50} is defined as the inhibitor concentration at 50% of the mean control activity (i.e., x when y=50%).
b. The relative IC_{50} is defined as the inhibitor concentration at the midpoint of the calculated maximum and minimum. By definition, the minimum for the 3-parameter logistic equation is zero. The relative IC_{50} is represented as the mean ± asymptotic standard error.
c. Values in parentheses represent the percent inhibition (mean ± standard deviation) observed at 100 µM.

Study SCY078-ADME-012 determined the IC50 and Ki values for the reversible inhibition of CYP2C8 and CYP3A4. Human liver microsomes from 50 individuals were incubated with marker substrates, at concentrations approximately equal to their apparent *K*m, in the presence or absence of ibrexafungerp.

Ibrexafungerp was a potent inhibitor of CYP2C8-mediated N-desethyl-amodiaquine activity and CYP3A-mediated midazolam-1'-hydroxylation, activity with IC50 values of 0.3 and 4.2 µM, respectively. The estimated IC50 value of ibrexafungerp for CYP3A-mediated testosterone-6β-hydroxylation activity was 29 µM (Table 16-16).

Ibrexafungerp inhibited CYP2C8-mediated N-desethyl-amodiaquine formation with a Ki value of 0.15 µM, and CYP3A mediated 1'-hydroxymidazolam formation with a Ki value of 2.1 µM. The mode of inhibition appeared to be mostly competitive for both isoforms (Table 16-17).

Table 16-16. Estimated IC50 Values for Reversible Inhibition of CYP Enzymes by SCY-078 in Human Liver Microsomes

P450 Enzyme	Inhibitor	IC_{50} Values (µM)
CYP2C8	SCY-078	0.27 ± 0.01
CYP2C8	Quercetin	0.82 ± 0.02
CYP3A (midazolam-1'-Hydroxylation)	SCY-078	4.22 ± 0.37
CYP3A (midazolam-1'-Hydroxylation)	Ketoconazole	0.01 ± 0.0005
CYP3A (testosterone-6β-Hydroxylation)	SCY-078	29.0 ± 6.91
CYP3A (testosterone-6β-Hydroxylation)	Ketoconazole	0.03 ± 0.001

Note: IC_{50} values = mean ± standard deviation with triplicate

Table 16-17. Ki Values and Mode of Inhibition of CYP Enzymes by SCY-078 in Human Liver Microsomes

P450 Enzyme	Metabolite Monitored	K_i Values (μM)	Mode of Inhibition
CYP2C8	N-Desethylamodiaquine	0.15 ± 0.01	Mostly Competitive
CYP3A	1'-Hydroxymidazolam	2.05 ± 0.17	Competitive

Note: Incubations were started with the addition of a NADPH solution at 37 °C
Incubation time: 10 mins for CYP2C8 and 5 mins for CYP 3A-midazolam
Microsomal protein concentrations: 0.1 mg/mL

The Effect of a Strong CYP3A Inhibitor on Ibrexafungerp
Study SCY078-ADME-065 evaluated the effect of ritonavir on the metabolism of ibrexafungerp in human hepatic chromosomes. The results indicated that ibrexafungerp was metabolized by HLMs in a NADPH-dependent manner. Ritonavir demonstrated inhibition of metabolism of ibrexafungerp as higher AUC values were observed in the presence of ritonavir. The inhibition was dependent on the concentrations of ritonavir and the concentrations of ibrexafungerp, with maximal inhibition at 0.18 μM of ritonavir.

Compared to the vehicle control, the maximal AUC in the presence of ritonavir was 114, 112, and 99.7% at 3.75, 7.5, and 15 μM ibrexafungerp, respectively. Ketoconazole (a strong CYP3A inhibitor) demonstrated marked inhibition at 3.75 μM of ibrexafungerp. Compared to the vehicle control, the AUC in the presence of ketoconazole (1 μM) was 114, 113, and 98.4% at 3.75, 7.5, and 15 μM ibrexafungerp, respectively.

In Vitro Induction of CYP1A2, CYP2B6 and CYP3A4
Studies PK002 and SCY078-ADME-026 evaluated the induction potential of ibrexafungerp.

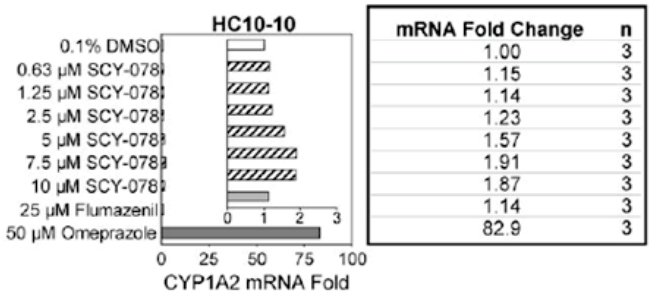
In Study PK002, the inducible effects of ibrexafungerp were evaluated in pooled human hepatocytes. Ibrexafungerp was not an agonist of human PXR in vitro (EC50 >30 μM with 9.7% activation relative to rifampicin control at 10 μM). In human hepatocytes, ibrexafungerp did not induce CYP3A4 or CYP1A mRNA expression or activity significantly, when compared to CYP-specific reference inducers (rifampicin or omeprazole, respectively).

In SCY078-ADME-026, three cryopreserved preparations of cultured human hepatocytes from three separate livers were treated once daily for two consecutive days with a vehicle control, negative control, one of six concentrations of ibrexafungerp (0.63, 1.25, 2.5, 5, 7.5 or 10 μM) or one of three known human CYP inducers, namely, omeprazole (50 μM), phenobarbital (750 μM) and rifampin (20 μM).

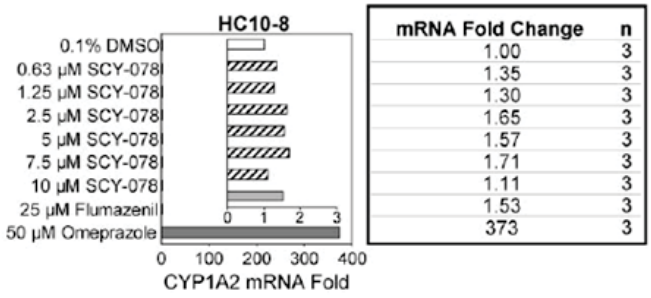
Ibrexafungerp had little or no effect on CYP1A2, CYP2B6 or CYP3A4 mRNA levels with two exceptions. Treatment of culture HC7-8 with 10 μM ibrexafungerp caused an increase of 6.55-fold change. However, this increase was 71.8% as effective as the positive control

phenobarbital (Figure 5). Treatment of culture HC7-8 with 10 µM ibrexafungerp caused an increase of 4.25 fold change. This increase was 1.37% as effective as the positive control rifampin (Figure 6). For both cultures, the concentration tested (10 µM) is substantially higher than the clinically relevant concentration and is not likely to be significant.

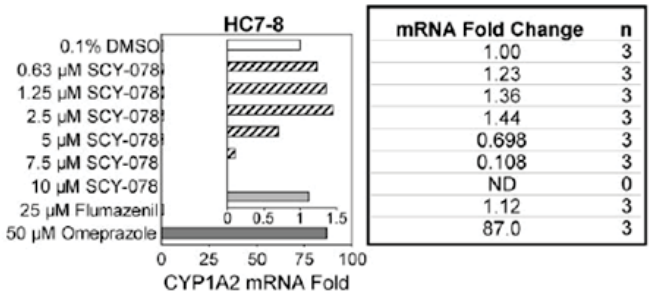
Figure 4. CYP1A2 fold change: The effect of treating cultured human hepatocytes with ibrexafungerp on CYP1A2 mRNA levels



mRNA Fold Change	n
1.00	3
1.15	3
1.14	3
1.23	3
1.57	3
1.91	3
1.87	3
1.14	3
82.9	3



mRNA Fold Change	n
1.00	3
1.35	3
1.30	3
1.65	3
1.57	3
1.71	3
1.11	3
1.53	3
373	3



mRNA Fold Change	n
1.00	3
1.23	3
1.36	3
1.44	3
0.698	3
0.108	3
ND	0
1.12	3
87.0	3

n Number of replicates
ND Not determined
Fold change values are relative to vehicle control, normalized to GAPDH.

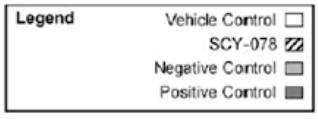


Figure 5. CYP2B6 fold change: The effect of treating cultured human hepatocytes with ibrexafungerp on CYP2B6 mRNA levels

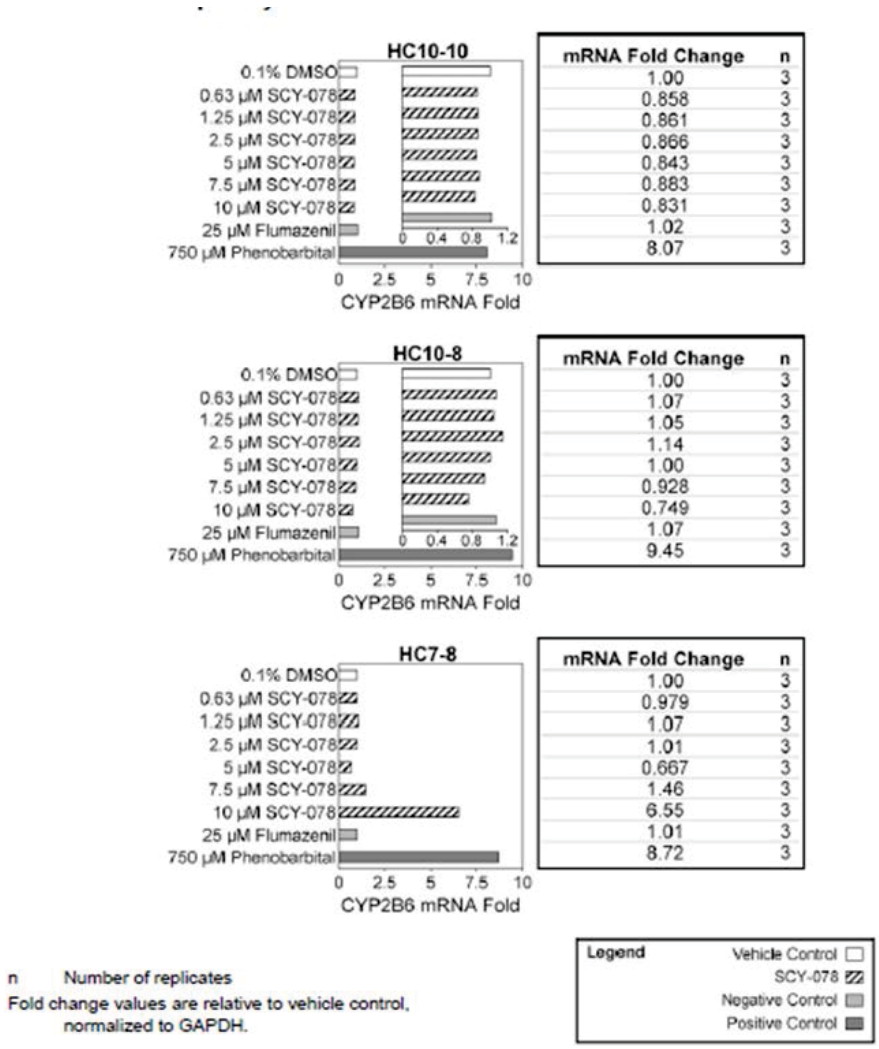
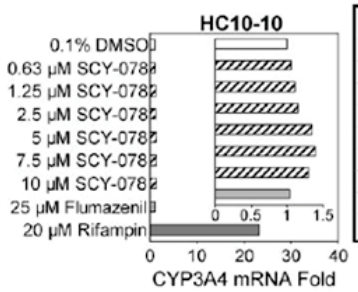
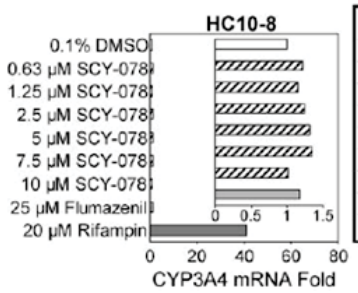


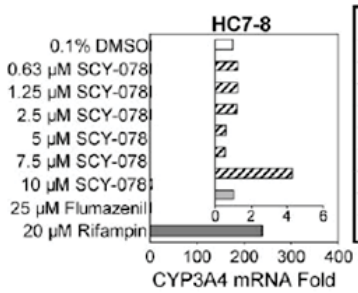
Figure 6. CYP3A4 fold change: The effect of treating cultured human hepatocytes with ibrexafungerp on CYP3A4 mRNA levels



mRNA Fold Change	n
1.00	3
1.05	3
1.11	3
1.15	3
1.35	3
1.39	3
1.30	3
1.03	3
23.1	3



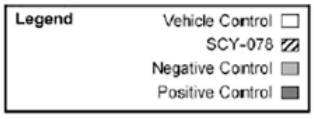
mRNA Fold Change	n
1.00	3
1.22	3
1.16	3
1.25	3
1.31	3
1.35	3
1.01	3
1.17	3
41.1	3



mRNA Fold Change	n
1.00	3
1.24	3
1.26	3
1.20	3
0.579	3
0.565	3
4.25	3
1.03	3
239	3

n Number of replicates

Fold change values are relative to vehicle control, normalized to GAPDH.



In Vitro Inhibition of UGT Enzymes

Study SCY078-ADME-057 evaluated the inhibitory effect of ibrexafungerp (up to 100 µM) on UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 using pooled human liver microsomes. Inhibition was determined by quantifying the UGT-specific probe substrate glucuronidated metabolite using LC-MS/MS analysis. Recombinant UGT2B15 supersomes were used to assess ibrexafungerp inhibitor effects on UGT2B15.

Ibrexafungerp inhibited UGT1A1, UGT1A3, and UGT1A4 with IC50 values of 26.2, 19.5, and 9.84 µM, respectively. Ibrexafungerp showed inhibition of UGT1A6 and UGT2B7, but the IC50 value could not be calculated and was estimated to be >100 µM (the highest concentration tested). Ibrexafungerp inhibited UGT2B15 with an IC50 value of 2.19 µM. Ibrexafungerp showed no inhibition of UGT1A9. All known selective UGT inhibitors included as positive controls

showed marked inhibition of the corresponding UGT enzymes, demonstrating the validity of the study results.

Reviewer Comment: These results are not expected to be clinically significant since the IC50 values for the inhibitory effect of ibrexafungerp on UGT enzymes are significantly higher than the anticipated clinical Cmax of ibrexafungerp.

Table 16-18. Summary of Inhibition of Human Liver UGTs by Ibrexafungerp

Study	SCY078-ADME-057		
Analyte	Ibrexafungerp		
Dose	0, 0.1, 0.5, 1, 5, 10, 25, 50, 100 µM		
Test system	Human liver microsomes		
UGT	Substrate	Inhibition	IC_{50} (µM)
1A1	Estradiol	Yes	26.2
1A3	Chenodeoxycholate	Yes	19.5
1A4	Trifluoperazine	Yes	9.84
1A6	Serotonin	Yes	>100
1A9	Propofol	No	ND
2B7	3'-Azido-3'-deoxythymidine	Yes	>100
2B15	7-Hydroxy-4-(trifluoro-methyl) coumarin	Yes	2.19

IC_{50}=median inhibitory concentration; ND=not determined; UGT=uridine 5'-diphospho-glucuronosyltransferase

Transporter Substrate Potential

Ibrexafungerp as a Substrate of P-glycoprotein

Study PK002 evaluated the potential for ibrexafungerp to act as a substrate for the P-gp transporter using LLC-PK1 cells transfected with the human or mouse P-gp genes, *Mdr1* or mouse *Mdr1a*, respectively. Verapamil was used as a probe substrate (positive control) for P-gp transport with basolateral to apical (B to A) / apical-to-basolateral (A to B) efflux ratios of 4.6 (mouse) and 5.6 (human), respectively. Ibrexafungerp was a substrate for the mouse and human P-gp transporter in vitro with efflux ratio of 3.2 (mouse) and 4.4 (human), respectively.

Additionally, ibrexafungerp was evaluated for its potential to act as a substrate of P-gp in Caco-2 cell monolayers in Study SCY078-ADME-014. Apparent permeability coefficients (Papp) of ibrexafungerp were determined over the range of drug concentrations from 0.5 to 20 µM in both AB and BA directions. Additional incubations were conducted in the presence of the P-gp inhibitors such as GF918 (2 µM) and verapamil (100 µM) to confirm whether efflux, if present, was mediated by P-gp. The value for efflux ratio of ibrexafungerp at 5 µM was decreased from 6.0 to 2.4 and 2.2 in the presence of GF918 (2 µM) and verapamil (100 µM), respectively, indicating that P-gp is involved in ibrexafungerp transport across Caco-2 cell monolayers.

Ibrexafungerp as a Substrate of BCRP or MRP2 Transporters

Study SCY078-ADME-004 assessed the potential for ibrexafungerp to act as a substrate for the BCRP or MRP2 transporters. The accumulation of ibrexafungerp in transporter-expressing vesicles in the presence and absence of ATP was evaluated using LC-MS/MS analysis. The substrate potential of ibrexafungerp for human uptake transporters OATP1B1 and OATP1B3 was evaluated by measuring the accumulation of drug in transporter-expressing or control

human embryonic kidney (HEK)293 cells. The accumulation of ibrexafungerp in BCRP and BRP2 vesicles and OATP1B1 and OATP1B3 cells was similar to control values and was not affected by the positive control inhibitors of each transporter indicating that ibrexafungerp is not a substrate of BCRP, MRP2, OATP1B1, or OATP1B3.

Ibrexafungerp as a Substrate of Solute Carrier Transporters
Study SCY078-ADME-056 evaluated ibrexafungerp as a substrate for OAT1 and OAT3, OCT2, and Multidrug and Toxin Extrusion (MATE)1 and MATE2-K transporters using HEK293 cells transiently transfected to express each key SLC transporter. Vector-transfected HEK293 cells served as a control. The fold uptake was <2 for transporters tested in the absence and presence of selective inhibitors for OAT1, OAT3, OCT2, MATE1, or MATE2-K. Therefore, ibrexafungerp was not considered a substrate of human uptake transporters tested in this study.

Transporter Inhibition Potential
Study SCY078-ADME-014 evaluated the potential of ibrexafungerp to act as an inhibitor of P-gp in Caco-2 cell monolayers using digoxin (5 µM), a probe P-gp substrate, in the absence or presence of ibrexafungerp (0.63 to 20 µM). Ibrexafungerp showed a concentration dependent inhibitory effect on P-gp mediated digoxin efflux with an IC50 value of 7.0 µM and resulted in 90% inhibition of P-gp efflux at a concentration of 20 µM. The positive control inhibitor GF918 inhibited P-gp activity by 96% at the drug concentration of 2 µM.

Study SCY078-ADME-004 evaluated the potential of ibrexafungerp (0.1, 0.3, 1, 3, 10, 30 and 100 uM) to act as an inhibitor of P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and a Substrate of BCRP, MRP2, OATP1B1 and OATP1B3 in Caco-2 cell monolayers. Known inhibitors were included as positive controls in all experiments.

MDR1, BCRP, BSEP, MRP2 and OATP1B3-mediated transport of probe substrates were inhibited in the presence of ibrexafungerp in a concentration-dependent manner. The calculated IC50 values were 1.64 µM for MDR1, 11.5 µM for BCRP, 3.91 µM for BSEP and 20.9 µM for MRP2. The IC50 value for OATP1B3 in the initial experiment was 0.112 and 0.178 µM for the repeat. When the probe substrate was changed to pravastatin, the IC50 value was 0.335 µM. OATP1B1, OCT1, OCT2, OAT1 and OAT3-mediated transport of probe substrates were not inhibited by more than 50% in the presence of SCY-078 at the highest concentration studied (30 µM).

The accumulation of SCY-078 in BCRP and MRP2 vesicles and OATP1B1 and OATP1B3 cells was similar to the control and was not affected by the positive control inhibitor suggesting that ibrexafungerp is not a substrate of BCRP, MRP2, OATP1B1 or OATP1B3.

In Study SCY078-ADME-056, HEK293 cells transiently transfected to express key solute carrier (SLC) transporters, including OAT1 and OAT3, OCT2, and Multidrug and Toxin Extrusion (MATE)1 and MATE2-K were used to evaluate ibrexafungerp as an inhibitor of each transporter using probe substrates. Vector-transfected HEK293 cells served as a control. Uptake of the probe substrates by MATE1 and MATE2-K was conducted in the absence and presence

of ibrexafungerp (10 and 100 µM). The remaining activity was 67.8 and 26.0% of vehicle control at 10 and 100 µM ibrexafungerp, respectively, for MATE1. The remaining activity was 74.7 and 40.4% of vehicle control at 10 and 100 µM ibrexafungerp, respectively, for MATE2-K.

Ibrexafungerp was not a substrate of OAT1, OAT3, OCT2, MATE1, and MATE2-K but was an inhibitor of MATE1 and MATE2-K (Table 16-19).

The isoenzyme specific IC50 values could not be calculated from the data but were estimated to be between 10 and 100 µM. Cimetidine, a selective inhibitor of both MATE1 and MATE2-K, demonstrated marked inhibition in the same experiments and met the acceptance criteria, demonstrating the validity of the study.

Reviewer Comment: MATE-mediated DDIs are not of significant concern with ibrexafungerp since the drug does not undergo significant active renal secretion and renal toxicity is unlikely.

Table 16-19. Evaluation of Potential Ibrexafungerp Inhibition of Uptake Transporters

Study	SCY078-ADME-056		
Analyte	Ibrexafungerp		
Treatment	Net Uptake Activity (pmol/minute/mg protein)		Percent Activity Remaining
	Mean[a]	SD	
MATE1 ^{14}C-Tetraethylammonium (5 µM)			
Vector Control[b]	2.75	1.14	NA
Vehicle Control[b]	113	17.8	100
Ibrexafungerp (10 µM)	77.2	6.25	67.8
Ibrexafungerp (100 µM)	31.3	4.26	26.0
Cimetidine (100 µM)	1.91	0.134	-0.764
MATE2-K ^{14}C-Tetraethylammonium (5 µM)			
Vector Control[b]	2.78	1.16	NA
Vehicle Control[b]	41.8	4.93	100
Ibrexafungerp (10 µM)	31.9	4.13	74.7
Ibrexafungerp (100 µM)	18.5	4.60	40.4
Cimetidine (100 µM)	3.88	0.313	2.81

MATE=Multidrug and Toxin Extrusion; NA=not applicable; SD=standard deviation
a. Mean of three replicates, except controls which are mean of six replicates.
b. Final solvent content was 1% DMSO.
Note: Activities were normalized with the vector control values.

Clinical Drug-Drug Interaction Studies

Ibrexafungerp as a Victim of Drug Interactions

Study SCY-078-008 evaluated the effects of multiple doses of ketoconazole (a strong CYP3A4 and P-gp inhibitor) on the single dose pharmacokinetics of ibrexafungerp in healthy subjects.

- Period 1: Subjects were administered a single dose of 50-mg ibrexafungerp (or placebo) only.
- Period 2: Following a washout period of at least 7 days, the same subjects were administered ketoconazole 400 mg for 15 days starting at Day -1 with a single dose of 50-mg ibrexafungerp (or placebo) coadministered on Day 1.

Blood samples were obtained pre-dose and at selected time points up to 96 hours (Period 1) and 312 hours (Period 2) after administration of ibrexafungerp.

Reviewer Comment: The original study design stated that subjects would receive 100-mg of ibrexafungerp or placebo. However, after reviewing all safety and pharmacokinetic data from prior Phase 1 studies, the dose for this study was reduced to 50 mg to have an approximate 10-fold margin from the proposed clinical dose in light of a potentially significant increase in exposure of ibrexafungerp when co-administered with ketoconazole. Since the increase in ibrexafungerp AUC is roughly dose-proportional at single doses of 10 mg to 1600 mg and multiple daily doses of 300 mg to 800 mg (Studies SCY-078-001 and SCY-078-002), the use of 50 mg in this study is acceptable.

Ketoconazole increased ibrexafungerp AUC0-inf by 5.8-fold and Cmax by 2.5-fold after multiple dose administration of ketoconazole (Table 16-20).

Table 16-20. Summary of Statistical Analysis for Ibrexafungerp PK Parameters by Treatment Group

		LS Geometric Mean (95% CI)[a]			T_{max} (hr)[b]	$t_{1/2}$ (hr)[c]
Treatment	N	$AUC_{0-\infty}$ (nM•hr)	AUC_{0-24hr} (nM•hr)	C_{max} (nM)		
SCY-078 Alone	12	795.12 (628.00, 1006.72)	459.65 (380.05, 555.94)	36.13 (30.03, 43.47)	2.0 (1.0-6.0)	20.3 ± 3.3
SCY-078 + Ketoconazole	10	4579.06 (3536.06, 5929.69)	1474.90 (1197.53, 1816.53)	91.15 (74.44, 111.62)	6.0 (4.0-8.0)	38.4 ± 12.2
GMR[d]		5.76 (4.31, 7.69)	3.21 (2.54, 4.05)	2.52 (2.01, 3.17)		

Source: Table 14.2.2.1, Listing 16.2.6.2
[a] LS Geometric Mean and 95% CI for AUC and C_{max} were calculated based on linear model: log (PK Result)=treatment effect.
[b] Median (Min - Max)
[c] Harmonic Mean ± Pseudo SD
[d] Geometric Mean Ratio, SCY-078 + Ketoconazole/SCY-078 Alone (90% CI).

Study SCY-078-016 evaluated the effects of multiple doses of diltiazem (a moderate CYP3A4 inhibitor) on the multiple dose pharmacokinetics of ibrexafungerp. Sixteen healthy adult male subjects received a fixed sequence of Treatment A followed by Treatment B after a washout period of at least 14 days.

- Treatment A: 200 mg x 3 of ibrexafungerp (total dose of 600 mg) on Day 1 and 100 mg once daily of ibrexafungerp on Days 2 to 14
- Treatment B: 240 mg QD of diltiazem on Days -1 to 14, 200 mg x 3 of ibrexafungerp (total dose of 600 mg) on Day 1, and 100 mg daily of ibrexafungerp on Days 2 to 14

Diltiazem increased ibrexafungerp AUC by 2.5-fold and Cmax by 2.21-fold after multiple dose administration of diltiazem (Table 16-21).

Table 16-21. Summary of Statistical Analysis for SCY-078 by Treatment Per-Protocol Population

Treatment	N	LS Geometric Mean (95% CI)[a]			T_{max} (hr)[b]	$t_{½}$ (hr)[c]
		AUC_{0-24hr} (nM•hr)	C_{max} (nM)	C_{24} (nM)		
SCY-078 Alone	16	2452 (2135, 2816)	164.5 (146.6, 184.5)	58.58 (49.68, 69.07)	5.0 (3.0-6.0)	14.3 ± 3.2
SCY-078 + Diltiazem	15	6179 (5355, 7129)	363.2 (322.6, 408.9)	182.2 (153.7, 216.0)	5.0 (4.0-6.0)	20.7 ± 3.6
GMR[d]		2.52 (2.14, 2.97)	2.21 (1.93, 2.53)	3.11 (2.55, 3.79)		

Source: Table 14.2.1.2, Table 14.2.2.1 and Listing 16.2.6.2
[a] LS Geometric Mean and its 95% CI were calculated based on linear model: log (PK Result) =treatment effect
[b] Median (Min - Max)
[c] Harmonic Mean ± Pseudo SD
[d] Geometric Mean Ratio, GMR SCY-078+Diltiazem/SCY-078 Alone (90% CI) on Day 14.

Effect of Acid Reducing Agent on Ibrexafungerp Pharmacokinetics

Study SCY-078-015 was an open-label, four period, randomized, partial crossover study that evaluated the effect of multiple dose pantoprazole administration on single dose ibrexafungerp PK.

Reviewer Comment: In addition to the effect of pantoprazole, (b) (4) *Results from this study as they relate to bioavailability are included separately in this review. Recommendations regarding food effect were based on Study SCY-078-107 using the citrate salt formulation.*

Sixteen subjects participated in 4 treatment periods and the interval between successive doses was at least 7 days.

- Treatment A: Single dose of 500 mg ibrexafungerp capsule (5 x 100 mg capsule) in the fasted state
- Treatment B: Single dose of 500 mg ibrexafungerp tablet (2 x 250 mg tablet) in the fasted state
- Treatment C: Five consecutive daily doses of Protonix 40 mg delayed release tablet with a single dose of 500 mg ibrexafungerp tablet (2 x 250 mg tablet) co-administered (approximately 2.5 hours after pantoprazole dosing) on Day 1
- Treatment D: Single dose of 500 mg ibrexafungerp tablet (2 x 250 mg tablet) following a high-fat meal

Pantoprazole decreased the ibrexafungerp AUC0-inf and Cmax by approximately 25% and 20%, respectively, after single dose administration of 500 mg ibrexafungerp compared to ibrexafungerp alone (Table 16-22).

Table 16-22. Summary of Pharmacokinetic Parameters of Ibrexafungerp Tablet and Ibrexafungerp Tablet Co-administered with Pantoprazole

PK Parameter	MK-3118 Tablet (B)			MK-3118 Tablet + PPI (C)			Ratio (C/B)	
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI
$AUC_{0-\infty}$ (hr·ng/mL)[1]	15	7804.01	(6232.88 , 9771.17)	14	5904.40	(4485.05 , 7772.93)	0.757	(0.615 , 0.930)
AUC_{0-24hr} (hr·ng/mL)[1]	15	4548.43	(3704.80 , 5584.16)	14	3349.34	(2494.61 , 4496.93)	0.736	(0.589 , 0.921)
AUC_{0-last} (hr·ng/mL)[1]	15	7390.06	(5905.15 , 9248.37)	14	5543.21	(4160.61 , 7385.26)	0.750	(0.605 , 0.929)
C_{max} (ng/mL)[1]	15	372.45	(301.74 , 459.73)	14	290.15	(210.71 , 399.53)	0.779	(0.612 , 0.991)
C_{24hr} (ng/mL)[1]	15	103.73	(82.16 , 130.97)	14	80.45	(57.67 , 112.22)	0.776	(0.610 , 0.985)
T_{max} (hr)[2]	15	4.02	3.97 - 6.00	14	4.06	2.00 - 8.00	-	-
$t_{½}$ (hr)[3]	15	21.79	17.05%	14	22.64	22.52%	-	-

CI = confidence interval; CV = coefficient of variation; GM = geometric mean; GMR = geometric mean ratio; PK = pharmacokinetic; PPI = Proton Pump Inhibitor

1 Back-transformed least squares mean and CI from mixed effects model with unstructured covariance structure performed on natural log-transformed values

2 Median; minimum, maximum

3 Geometric Mean, CV%

Reviewer Comment: This study used a lower limit 90% CI for AUC0-inf GMR (with PPI / without PPI) of >0.60 to satisfy the hypothesis that the pharmacokinetics of ibrexafungerp were similar with or without a PPI based on the variability of ibrexafungerp exposure after oral administration. This is an acceptable approach given the AUC0-24 CV% of 32.21 and AUC0-inf CV% of 38.37 noted in healthy subjects who received the to-be-marketed formulation and recommended dose of ibrexafungerp for VVC (Study SCY-078-107). Based on the non-effect boundaries defined in this study, the DDI interaction with pantoprazole was not considered to be significant.

A decrease of 25% in exposure associated with coadministration of a PPI is not likely to be clinically significant given the overall variability of ibrexafungerp exposure among VVC patients is >20%.

Ibrexafungerp as a Perpetrator of Drug Interactions

The drug interaction studies evaluating the potential of ibrexafungerp as a perpetrator of drug interactions were conducted at doses and exposures higher than the recommended dose of ibrexafungerp for VVC. Given the higher doses evaluated in these studies and the single day treatment duration for VVC, the effect of ibrexafungerp on the pharmacokinetics of the substrates included herein are not considered to be clinically significant.

Ibrexafungerp as an Inhibitor of CYP3A4 and/or P-gp

Study SCY-078-103 evaluated ibrexafungerp PK after a single oral 2 mg dose of tacrolimus (a sensitive CYP 3A4 and P-gp substrate) on Day 1 and when co-administered with ibrexafungerp dosed to steady state.

In Cohort 1, Period 1, subjects were admitted to the clinical site on the evening of Day -1. Subjects were required to then fast for 10 hours prior to the Day 1 tacrolimus dose. The 24 subjects then received a single 2 mg dose of tacrolimus on Day 1 in a fasted state. Whole blood samples for tacrolimus were taken for 144 hours postdose. There was a 15-day wash-out period prior to the start of Cohort 1, Period 2.

In Cohort 1, Period 2, subjects were re-admitted to the clinical site on the evening of Day -1. Subjects were then required to fast for 10 hours prior to study drug administration. On Day 1, a single oral loading dose of 1250 mg ibrexafungerp citrate was administered in a fasted state. On Day 2, a single maintenance dose of 750-mg ibrexafungerp citrate was administered. On Day 3, subjects were administered a single dose of 2 mg tacrolimus and 750 mg of ibrexafungerp citrate. On Days 4 through 8, single maintenance doses of 750-mg ibrexafungerp were administered once daily. Subjects had whole blood samples taken for tacrolimus levels for 144 hours after the Day 3 dose. Blood samples for ibrexafungerp pharmacokinetics were also collected on Days 1 through 8.

Tacrolimus showed a 1.4-fold increase in AUC∞ and no effect on Cmax when given with ibrexafungerp compared to a single dose of tacrolimus given alone (Table 16-23).

Table 16-23. Summary of Statistical Analysis for Tacrolimus Co-administered with Ibrexafungerp Compared to Tacrolimus Administered Alone

Formulations[a]	N	AUC_{∞} (ng•h/mL)[b]	$AUC_{0\text{-}12hr}$ (ng•h/mL)[b]	$AUC_{0\text{-}24hr}$ (ng•h/mL)[b]	C_{max} (ng/mL)[b]	C_{12hr} (ng/mL)[b]	C_{24hr} (ng/mL)[b]	T_{max} (hr)[c]
Test (tacrolimus + ibrexafungerp)	23	116.9 (94.53, 144.7)	47.06 (38.98, 56.81)	63.22 (52.08, 76.73)	8.29 (6.93, 9.93)	1.71 (1.38, 2.13)	1.07 (0.86, 1.33)	2.0 (1.0-4.0)
Reference (tacrolimus alone)	23	82.50 (66.68, 102.1)	35.89 (29.73, 43.33)	46.16 (38.03, 56.03)	8.03 (6.71, 9.61)	1.03 (0.83, 1.28)	0.70 (0.56, 0.87)	2.0 (1.0-4.0)
GMR[d]	23	1.42 (1.25, 1.61)	1.31 (1.15, 1.49)	1.37 (1.21, 1.56)	1.03 (0.89, 1.20)	1.67 (1.45, 1.91)	1.54 (1.33, 1.77)	
P-value[e]								0.0022

Source: SCY-078-103 Table 14.2.3.1, Data Listing 16.2.6.3, and Data Listing 16.2.6.4

[a] Test - tacrolimus 2 mg coadministered with ibrexafungerp in Cohort 1, Period 2; Reference - tacrolimus 2 mg administered alone in Cohort 1, Period 1

[b] LS geometric Mean and its 95% CI were calculated based on linear mixed effects model: (log PK Result)= treatment + subject

[c] Median (Min - Max)

[d] GMR = geometric Means Ratio, GMR Test/Reference (90%CI)

[e] P-value is based on the Wilcoxon signed-rank test of the paired T_{max} values for each subject (note that despite identical median T_{max} values and ranges, 10 subjects have identical T_{max} on test and reference formulations, 11 subjects have longer (delayed) T_{max} with the test formulation, and 1 subject has a shortened T_{max} with test formulation).

Ibrexafungerp as an Inhibitor of CYP2C8

Study SCY-078-104 evaluated the effect of multiple doses of ibrexafungerp on the pharmacokinetics of rosiglitazone (a moderate sensitive CYP2C8 substrate). Twenty-four healthy subjects were randomized to a treatment sequence A/B or B/A.

- Treatment A = a single oral 4 mg dose of rosiglitazone given alone on Day 1
- Treatment B = a loading dose of oral 1250-mg ibrexafungerp citrate followed by a once daily dose of oral 750 mg ibrexafungerp for 7 additional days with a single 4 mg dose of rosiglitazone administered concurrently on Day 3.

After a 10-day washout period between treatments, subjects crossed over and received the alternate treatment.

Blood samples for rosiglitazone and its metabolite N-desmethylrosiglitazone, were obtained during Day 1 and Day 3 at pre-dose up to 120 hours post-dose. Trough blood samples were collected on Days 4, 5, 6, 7, and 8.

AUC∞ and Cmax were not altered following coadministration of ibrexafungerp citrate and rosiglitazone as compared to rosiglitazone alone. The major metabolite N-desmethylrosiglitazone was also not affected by co-administration of multiple doses of ibrexafungerp (Table 16-24).

Table 16-24. Summary of Statistical Analysis for Rosiglitazone Co-administered with Ibrexafungerp Compared to Rosiglitazone Administered Alone On Rosiglitazone

Treatment	N	$AUC_{0-\infty}$ (nM•hr)[a]	AUC_{0-last} (nM•hr)[a]	AUC_{0-24hr} (nM•hr)[a]	C_{max} (nM)[a]	T_{max} (h)[b]
Test (Rosiglitazone + Ibrexafungerp)	17	1451 (1334, 1578)	1439 (1323, 1566)	1417 (1306, 1537)	235.1 (211.9, 260.7)	1.0 (0.5 – 4.0)
Reference (Rosiglitazone Alone)	17	1461 (1344, 1589)	1451 (1333, 1579)	1442 (1329, 1565)	295.6 (266.5, 327.8)	0.53 (0.5 – 1.0)
GMR[c]	17	0.99 (0.90, 1.10)	-0.99 (0.90, 1.10)	0.98 (0.89, 1.08)	0.80 (0.70, 0.90)	
P-value[d]						0.0005

Source: SCY-078-104 Table 14.2.3.1, and Data Listing 16.2.6.5
[a] LS Geometric Mean and its 95% CI were calculated based on linear model: log(PK Result)=Sequence of Treatment, Treatment
[b] Median (Min-Max)
[c] GMR-Geometric Means Ratio, GMR Test/Reference (90% CI)
[d] The p value is calculated by Wilcoxon signed-rank test.

Reviewer Comment: Rosiglitazone is classified as a moderate sensitive CYP2C8 substrate rather than a sensitive CYP2C8 substrate.

Ibrexafungerp as an Inhibitor of P-gp
Study SCY-078-108 was a randomized, two-period crossover study that evaluated the effect of multiple doses of ibrexafungerp on the pharmacokinetics of dabigatran (a sensitive P-gp substrate) in healthy male subjects.

All subjects were admitted to the clinical site on Day -1 of each period , fasted overnight and remained in the clinical site until after the final procedures were completed. A minimum 10-day washout period was observed between the last dose in the first period and the first dose in the subsequent period

- Treatment A = Single oral 150 mg dose of dabigatran on Day 1 morning (AM).
- Treatment B = Twice daily (every 12 hours) oral doses of ibrexafungerp 750 mg on Day 1 and Day 2; and single oral AM doses of ibrexafungerp 750 mg on Day 3 and Day 4. On Day 3 a single 150 mg dose of dabigatran was administered one hour after the AM dose of ibrexafungerp.

Blood samples for dabigatran were collected on Day 1 in Treatment A and Day 3 in Treatment B at pre-dose and up to 48 hours post-dose. Blood samples for ibrexafungerp were collected on Days 1, 2, 3, and 4 at pre-dose, 1, 2, 4, and 6 hours post-dose in Treatment B.

Coadministration of dabigatran and ibrexafungerp led to an increase in AUC0-48hr and Cmax of 40% and 25%, respectively, compared to dabigatran administered alone.

Table 16-25. Statistical Analysis of Effect of Multiple Doses of Ibrexafungerp on the Single Dose PK Parameters of Dabigatran

PK Parameter (unit)	Geometric Least Squares Mean		Ratio ([Dabigatran + Ibrexafungerp]/Dabigatran)	
	Dabigatran	Dabigatran + Ibrexafungerp	Estimate	90% CI
AUC_{0-48} (h•ng/mL)	954.24	1337.12	1.40	(1.17, 1.67)
C_{max} (ng/mL)	102.07	128.10	1.25	(1.03, 1.53)
	Median (range)		P-value	
	Dabigatran	Dabigatran + Ibrexafungerp		
T_{max} (h)	2.00 (1.00, 4.00)	4.00 (3.00, 4.03)	0.0001	
$t_{1/2}$ (hr)	9.31 (6.74, 13.63)	9.47 (5.80, 14.41)	0.4668	

Source: SCY-078-108 Table 14.2.1.5, 14.2.1.6, 14.2.1.7, and Data Listing 16.2.6.2.1

Ibrexafungerp as an Inhibitor of OATP1B1 and OATP1B3 Transporters

Study SCY-078-115 was an open-label, randomized, two-period crossover study that evaluated the effect of oral ibrexafungerp on the pharmacokinetics of pravastatin (a substrate for OATP1B1 and OATP1B3) administered orally to healthy adult male subjects.

- Treatment A = Single oral 20-mg dose of pravastatin on Day 1 AM.
- Treatment B = Twice daily (every 12 hours) oral doses of ibrexafungerp 750 mg on Day 1 and Day 2; and on Day 3 a single oral AM dose of ibrexafungerp 750 mg followed by a single 20 mg dose of pravastatin administered one hour later.

All subjects were admitted to the clinical site on Day -1 in each period and fasted overnight. At least 10 days washout was observed between treatment groups.

Blood samples for pravastatin were collected on Day 1 in Treatment A and Day 3 in Treatment B at pre-dose and up to 24 hours post-dose. Blood samples for ibrexafungerp were collected on Days 1, 2, and 3 at pre-dose and up to 6 hours post-dose in Treatment B.

Coadministration with ibrexafungerp led to an increase in pravastatin AUC0-24hr and Cmax of approximately 2.8-fold and 3.5-fold, respectively (Table 16-26).

Table 16-26. Statistical Analysis of Effect of Multiple Doses of Ibrexafungerp on the Single Dose PK Parameters of Pravastatin

PK Parameter (unit)	N	Geometric Least Squares Mean		Ratio ([Pravastatin + Ibrexafungerp]/Pravastatin)	
		Pravastatin	Pravastatin + Ibrexafungerp	Estimate	90% CI
$AUC_{0\text{-}24hr}$ (h•ng/mL)	26	45.22	127.32	2.82	(2.28, 3.48)
C_{max} (ng/mL)	26	15.80	54.65	3.46	(2.64, 4.54)
		Median (range)		P-value	
		Pravastatin	Pravastatin + Ibrexafungerp		
T_{max} (h)	26	1.00 (1.00, 3.00)	1.00 (0.97, 3.00)	0.5862	
$t_{1/2}$ (hr)	25[1]	2.31 (1.16, 4.36)	2.42 (1.31, 25.11)	0.0930	

Source: SCY-078-115 Tables 14.2.1.5, 16.2.1.6, 14.2.1.7, and Data Listing 16.2.6.2.1
[1] N=25 pravastatin + Ibrexafungerp Treatment; $t_{1/2}$ could not be determined in Subject # (b) (6)
Treatment A (Reference) = Single oral 20-mg dose of pravastatin on Day 1 AM.
Treatment B (Test) = Twice daily (BID) oral doses (Q12H) of ibrexafungerp 750 mg on Day 1 and Day 2; and single oral AM doses of ibrexafungerp 750 mg on Day 3. On Day 3 a single 20-mg oral dose of pravastatin was administered one hour after the AM dose of ibrexafungerp.

Food Effect

Food effect was assessed in three studies, SCY-078-015, SCY-078-102, and SCY-078-107. Only Study SCY-078-107 evaluated the to-be marketed formulation and dose for the VVC indication and is included in this section of the review.

The primary objectives of Study SCY-078-107 were to evaluate the PK, safety and tolerability of single and multiple-dose ibrexafungerp from two oral formulations (the citrate salt tablet and the lipid-dispersion oral tablet), and to determine the effect of a high-fat meal on the PK following single dose administration of each formulation. The Applicant also evaluated the effect of a low-fat meal for each formulation.

Reviewer Comment: This review will focus on the results of the food effect for the to-be-marketed citrate salt formulation since the lipid-dispersion formulation was not continued in development.

For Part I, Panel A, subjects were given Treatment A, B, C or D in Period 1 and then crossed over to an alternate treatment in Periods 2 – 4 after a 10-day washout period. All Panel A subjects were given Treatment E during Period 5.

- Treatment A = Oral dose of 600-mg (4 x 150-mg tablets) citrate salt tablet in the fasted state
- Treatment B = Oral dose of 100-mg (1 x 100-mg tablets) lipid-dispersion tablet in the fasted state
- Treatment C = Oral dose of 300-mg (3 x 100-mg tablets) lipid-dispersion tablet in the fasted state.
- Treatment D = Oral dose of 600-mg (6 x 100-mg tablets) lipid-dispersion tablet in the fasted state.

- Treatment E = Oral dose of 300-mg (3 x 100-mg tablets) lipid-dispersion tablet (E1) or 300 mg (2 x 150-mg tablets) citrate salt tablet (E2) in the fed state (following a high-fat breakfast).

For the citrate salt tablet formulation, the food effect was evaluated by a dose-normalized comparison of subjects who crossed-over from Treatment A (600 mg citrate salt tablet in the fasted state, n=9 subset) to Treatment E2 (300 mg citrate salt in the fed state, n=9). Dose-normalization was performed with results presented per 300 mg.

For Part II Panel B, subjects consumed a standard low-fat meal beginning 30 minutes prior to each dose of Treatment F, 300 mg (2 x 150-mg) of twice daily of the citrate salt tablet administered fed for each dose on Day 1. Subjects were given Treatment F or G in Period 1 and then crossed over to the alternate treatment in Period 2 after a 10-day washout period.

- Treatment F = Oral doses of 300 mg (2 x 150-mg) twice daily of the citrate salt tablet, were administered fed (after a standard low-fat meal) for each dose on Day 1.
- Treatment G = Oral doses 200 mg (2 x 100-mg) twice daily X 1 day of the lipid-dispersion tablet), were administered fed (after a standard low-fat meal) for each dose on Day 1.

The effect of dose administration of the citrate salt tablet following a standard low-fat meal was examined by comparing the 600-mg citrate salt tablet in the fasted state in Panel A, Treatment A subjects versus the 300-mg citrate salt tablet in Panel B, Treatment F subjects (fed).

Table 16-27. High-Fat and Low-Fat Breakfast Content and Composition

Meal Type	Contents	Calories	Fat
High-Fat Breakfast	2 fried/scrambled eggs 2 strips bacon 2 slices toast/2 pats butter 113 g (4 oz) hash browns 240 mL whole milk	800-1000 total 150 from protein 250 from carbohydrates 500-600 from fat	50%
Low-Fat Breakfast	2 slices white bread 1 tsp low-fat margarine 1 Tbs jelly 5 oz skim milk 5 oz orange juice	373 total	20%

A food effect was observed when the ibrexafungerp citrate salt tablet was administered following a standard high-fat breakfast, based on AUC0-inf increasing 38% and Cmax increasing 32% for ibrexafungerp dosing in the fed state compared with ibrexafungerp dosing in the fasted state (Table 16-28).

Table 16-28. Summary of Statistical Analyses for Ibrexafungerp- Panel A Food Effect Comparison for the Citrate Salt Tablet following Standard High Fat Meal

Ibrexafungerp Formulation	N	AUC_{0-inf} (h*nM)	C_{max} (nM)	Tmax (h)
Citrate Salt Tablet- Dose Normalized (AUC_{0-inf} and C_{max}/300 mg Dose), Crossover Subjects Only (Treatment A and E)				
300 mg -fed (E2)	9	11052 (7907, 15449)	420.6 (310.9, 586)	6 (6-8)
600 mg- fasted (A)	9	7997 (5721, 11179)	318 (228.2, 443)	4 (2-6)
GMR- E2/A Comparison		1.38 (0.95, 2.02)	1.32 (0.91, 1.92)	
p-value				0.0156

Source: Study SCY-078-107

A food effect was also observed when the ibrexafungerp citrate salt tablet was administered following a standard low-fat breakfast, based on AUC increasing approximately 27-83% for ibrexafungerp dosing in the fed state compared with ibrexafungerp dosing in the fasted state (Table 16-29).

Table 16-29. Summary of Statistical Analyses for Ibrexafungerp Food Effect Comparison for Panel A Citrate Salt Treatment A, 600 mg (4 x 150-mg) Fasted Versus Panel B Citrate Salt Treatment F following Standard Low-Fat Meal

SCY-078 Formulations[a]	N	$AUC_{0-\infty}$ (h•nM per 600-mg daily dose)[b]	AUC_{0-24hr} (h•nM per 600-mg daily dose)[b]	C_{max} (nM per 600-mg daily dose)[b]
Panel B vs. Panel A				
Citrate Salt 300 mg BID x 2 (F) – fed	12	27687 (21505, 35647)	10852 (8684, 13561)	568.3 (458.8, 704.0)
Citrate Salt 600 mg AM x 1 (A) – fasted	20	16074 (13216, 19549)	8555 (7199, 10167)	628.9 (532.8, 742.3)
GMR[c] – F/A comparison		1.72 (1.32, 2.25)	1.27 (1.00, 1.60)	0.90 (0.72, 1.13)
SCY-078 Formulations[a]	**N**	**AUC_{0-12hr} (h•nM per 300-mg dose)[b,e]**	**C_{12hr} (nM per 300-mg dose)[b,e]**	**T_{max} (h)**
Panel B vs. Panel A				
Citrate Salt 300 mg BID x 2 (F) – fed	12	4741 (3825, 5876)	303.4 (241.7, 380.8)	6.0 (2.00 – 6.00)
Citrate Salt 600 mg AM x 1 (A) – fasted	20	2597 (2199, 3066)	188.4 (158.0, 224.7)	6.0 (2.00 – 12.00)
GMR[c] – F/A comparison		1.83 (1.46, 2.29)	1.61 (1.27, 2.05)	
P-value[d]				0.6318

Source: Table 14.2.3.3.1, Listing 16.2.6.2.1 and Listing 16.2.6.2.3

[a] Panel A, Treatment A = Citrate salt tablet 4x150mg (600mg total dose given in the morning of Day 1); Panel B, Treatment F = Citrate salt tablet 2x150mg (300mg) BID x 2 doses (600mg total daily dose on Day 1).

[b] LS geometric Mean and its 95% CI were calculated based on linear mixed effects model: (log PK Result)= treatment + period

[c] GMR= Geometric Means Ratio, GMR Test/Reference (90% CI).

[d] p-value based on Wilcoxon rank sum test.

[e] AUC_{0-12hr} and C_{12hr} values were dose-normalized for Treatment A by dividing original values by 2, meaning AUC_{0-12hr} and C_{12hr} values following the 600-mg morning dose were divided by 2. The Treatment F values were reported as original values since the morning dose was 300 mg.

Reviewer Comment: Subjects who received the citrate salt tablet in the fasted state were not subsequently enrolled to receive the study drug with a low-fat meal following an adequate washout period. This lack of a cross-panel comparison limits the interpretation the food effect following a low-fat meal. Further, there is significant variability in the AUC values reported. The labeling of ibrexafungerp will rely on the food effect data following administration of a high-fat meal in Part 1, Panel A where subjects received ibrexafungerp in the fasted and fed state following a 10-day washout period.

The most common treatment-emergent and treatment-related AEs in this study were diarrhea and nausea occurring mainly in the 600 mg dose with citrate salt tablets in the fasted state.

Bioavailability/Bioequivalence

Several oral dose formulations were used in Phase 1 studies, including a (b) (4) phosphate capsule (10 mg, 100 mg), a phosphate tablet (100 mg, 250 mg) and a citrate tablet (150 mg and 250 mg).

Study SCY-078-102 was an open-label, three-period, randomized, partial-crossover study that compared the plasma pharmacokinetic parameters after a single oral dose of 500 mg (2 x 250-mg tablets) of the citrate tablet formulation and the phosphate tablet formulation in a fasted state and following a high fat meal. To estimate the relative bioavailability of the ibrexafungerp phosphate formulation compared to the citrate formulation administered in the fasted state

- Treatment A = Oral doses of 500 mg (2×250-mg tablets) ibrexafungerp phosphate tablets in the fasted state
- Treatment B = Oral doses of 500 mg (2×250-mg tablets) ibrexafungerp citrate tablets in the fasted state
- Treatment C = Oral doses of 500 mg (2×250-mg tablets) ibrexafungerp citrate tablets in the fed state (following a high-fat breakfast)

Blood samples for ibrexafungerp concentration were collected predose up to 96 hours postdose.

Reviewer Comment: The Applicant's food effect recommendation is based on the results of Study SCY-078-107 using the to be marketed dose and formulation (See Food Effect). This review will focus on the fasted data used to evaluate bioavailability.

Single oral doses of Ibrexafungerp 500 mg (2×250-mg tablets) citrate and phosphate tablets administered in the fasted state had comparable bioavailability based on Test/Reference GMR (90% CI) results for $AUC_{0-\infty}$ of 1.00 and C_{max} of 1.02 (Table 16-30).

Table 16-30. Summary of Statistical Analysis for Ibrexafungerp 250 mg x2 Tablets Administered Fasting by Formulation

Summary of Statistical Analysis for SCY-078 250 mg x 2 Tablets Administered Fasting by Formulation Biocomparison PK Population

Formulations	n	$AUC_{0-\infty}$ (h*nM)[a]	AUC_{0-last} (h*nM)[a]	AUC_{0-24hr} (h*nM)[a]	C_{max} (nM)[a]	C_{24hr} (nM)[a]	T_{max} (h)[b]
Citrate Tablets (Test)	23	12046 (9441, 15369)	11399 (8925, 14559)	7212 (5799, 8971)	569.0 (469.7, 689.3)	151.6 (117.4, 195.8)	4.0 (2.0-6.0)
Phosphate Tablets (Reference)	23	12025 (9424, 15343)	11423 (8943, 14589)	7081 (5693, 8807)	559.8 (462.1, 678.1)	156.0 (120.8, 201.4)	6.0 (2.0-6.0)
GMR[c]	23	1.00 (0.75, 1.34)	1.00 (0.75, 1.33)	1.02 (0.79, 1.32)	1.02 (0.81, 1.27)	0.97 (0.72, 1.31)	
P-value[d]							0.0786

The 250 mg strength citrate salt tablet was used to support clinical studies in invasive systemic fungal infections. The 250 mg and 150 mg citrate salt tablet were shown to have identical quantitative composition (%w/w) and similar in vitro dissolution profiles.

16.4.3. Pharmacometrics Review

Population PK analysis

Review Summary

The applicant's population pharmacokinetics (PPK) analysis for ibrexafungerp is acceptable, to support descriptive labeling of ibrexafungerp PK as outlined in Table 16-31.The applicant's final PPK model described the observed ibrexafungerp plasma concentrations. Parameter estimates for the final model were estimated with relatively moderate precision with relative standard error (RSE) for total clearance (CL, 27%), volume of distribution in central compartment (V2, 21.2%), volume of distribution in peripheral compartment (V3), the inter-compartmental clearance (Q3), bioavailability (F1, 26.8%) and covariates (food on F1, age on V3, vulvovaginal candidiasis on F1), and shrinkages for inter-individual variability on CL and V2 were10.9% and 63.8% respectively. The goodness-of-fit plots showed a good agreement between the observed and the individual predicted concentrations without any obvious bias over time or predicted concentrations. The prediction-corrected visual predictive check (pcVPC) plots showed a good agreement between the observed and the simulated concentrations.

Table 16-31. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about	**Intrinsic factor**	Based on a population pharmacokinetic analysis, the model predicts that 300 mg twice a day for 2 doses under fasted conditions achieves a mean (%CV) AUC exposure of 6832 (15%) ng•hr/mL and	The statement is acceptable, based on the final model parameters, simulation and statistical assessment.

intrinsic and extrinsic factors		C_{max} of 435 (15%) ng/mL for patients with VVC. After oral administration of BREXAFEMME in healthy volunteers, ibrexafungerp generally reaches maximum plasma concentrations 4 to 6 hours after single and multiple dosing.	
	Extrinsic factor		
Derive exposure metrics for Exposure-response analyses	Cmax, AUC		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses. However, The shrinkage for V2 was 63.8% and therefore the post-hoc individual estimates of V2 should be used with caution.
Predict exposures at alternative dosing regimen	NA		NA

*Detailed statistical explanation of covariates was shown in **1.7**.*

Introduction

The primary objectives of applicant's analysis were to:

- Characterize the structural pharmacokinetic (PK) model and quantify the population variability in the PK parameters of ibrexafungerp.
- Describe the effects of intrinsic and/or extrinsic factors on ibrexafungerp exposure.
- Generate individual clearance estimates for patients in Phase 1 and 2 studies that can be used for subsequent exposure-response analyses

Model development

Data

PPK models were developed by the applicant to describe the PK of ibrexafungerp using a total of 1264[31] plasma concentration data of ibrexafungerp from 101 subjects, from phase 1 studies (SCY-078-102, SCY-078-107) in healthy subjects and one phase 2 study (SCY-078-204) in

[31] [31] *Applicant's scy-078-pop-pk-003 Report on Page 20 (link).*

patients with vulvovaginal candidiasis (VVC), with ibrexafungerp citrate tablet that is the dosage form intended for commercialization. For healthy subjects, nominal doses of 300 mg to 600 mg were included in the population PK analysis because these were relevant to the dose range intended for clinical use, and PK data from VVC patients were included in the analysis with nominal doses of 150 mg to 750 mg. The dosing regimen and PK sampling for the clinical studies included PPK analysis were summarized in Table 16-32.

Table 16-32. Summary of Clinical Study Designs

Study ID	Study Title	Phase	Population (N)	Dosing Regimen	PK Sampling Schedules
102	A Phase I, Three Period, Open-Label, Oral Biocomparison Study of Two Formulations of SCY- 078 with a Food Effect Period in Healthy Subjects	1	healthy (23)	500 mg (2 x 250 mg QD) PO SCY-078 citrate tablet (fasted) (N=23) 500 mg (2 x 250 mg QD) PO SCY-078 citrate tablet (high fat breakfast) (N=22)	Pre-dose, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hr
107	A Phase 1, Open-Label, Crossover, Single- and Multiple-Dose, Oral, Biocomparison Study of Two SCY-078 Formulations in Healthy Subjects	1	healthy (32)	Panel A: Oral dose of 600 mg (4 x 150 mg QD) (citrate tablet, fasted) (N=20) Oral dose of 300 mg (2 x 150 mg QD) citrate tablet, fed with high-fat breakfast) (N=9) Panel B: Oral doses of 300 mg BID (2 x 150 mg Q12) on Day 1 (citrate tablet, fed regular meal) (N=12)	Panel A Periods 1-5: Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 hours post-dose Panel B Periods 1 and 2: Pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours post-dose after the AM dose
	A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy,	2	Vulvovaginal Candidiasis (46)	Treatment Group 1: oral SCY-078 750 mg QD (5 x 150 mg QD) on Day 1 only (N=9) Treatment Group 2: oral SCY-078 300 mg BID (2 x 150 mg Q12) on Day 1 only (N=9)	Day 3: Pre-dose, 2-6 hr postdose of either morning or evening dose

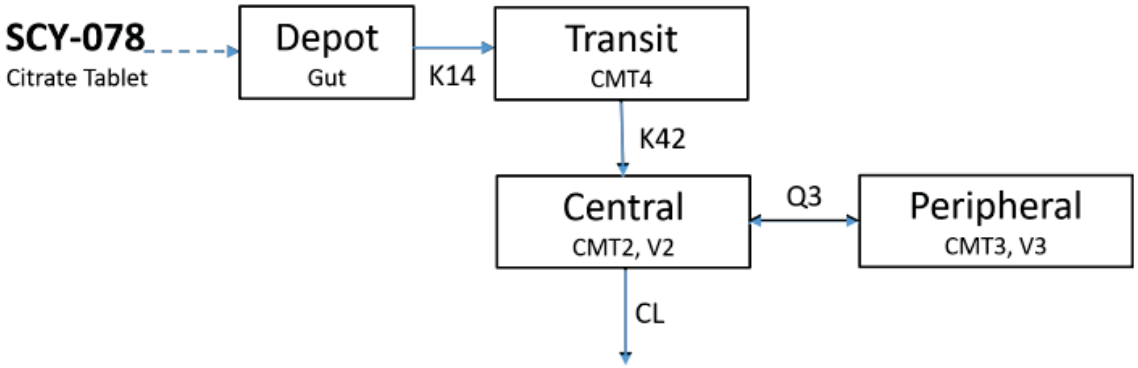
204	Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Vulvovaginal Candidiasis (DOVE)			Treatment Group 3: oral SCY-078 450 mg BID (3 x 150 mg Q12) on Day 1 only (N=8) Treatment Group 4: oral SCY-078 150 mg BID (1 x 150 mg Q12) on Days 1 to 3 (N=9) Treatment Group 5: oral SCY-078 300 mg BID (2 x 150 mg Q12) on Days 1 to 3 (N=11) For all treatment groups, ibrexafungerp must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.	Day 10 (± 2): any time of day as close to Day 10 as possible

N = number of subjects; PO = per oral; QD = once daily; BID = twice daily;
Source: Applicant's scy-078-pop-pk-003 Report, Table-1-1 on Page 2 (link).

Base model

The base model was a two-compartment plus one transit compartment PK model with delayed first order absorption and first-order elimination from the central compartment. The 2-compartment model included the following parameters: K14, K42, CL, V2, V3 and Q3 as following Figure 7.

Figure *7*. Schematic of the PK model for ibrexafungerp



Source: Applicant's scy-078-pop-pk-003 Report on Page 27 (link).

Inter-individual variability was built in models assuming a log-normal distribution for patient level random effects and all random effects were independent.

Intra-individual variability was a combined additive and proportional error model.

Model evaluation and selection were based on the point estimates of PK parameters, their respective relative standard errors and standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0) by bootstrap, successful model convergence, and diagnostic plots (pcVPC).

Covariate analysis

Covariate parameters include vulvovaginal candidiasis on F1 and V3, daily total dose on F1 and K42, nominal dose on V2 and CL, age on V3, and food effect on F1

Covariates (proportional model) were assessed for covariates with forward selection criteria of the significant level of 0.01 based on $\chi 2$ test ($p < 0.01$, a decrease in OBJ > 6.64 for one degree of freedom) and backward deletion criteria with the significance level of 0.001 based on $\chi 2$ test ($p < 0.001$, an increase in OBJ > 10.83 for one degree of freedom)

Final Model

The final population PK model is a 2-compartment model with delayed first-order absorption as parameterized with F1, CL, V2, V3, Q3, K14 and K42 for ibrexafungerp, with an exponential model for inter-individual variability, and a combined additive and proportional error model for intra-individual variability. All the final model parameter estimates are listed in Table 16-33. Meanwhile the goodness-of-fit plots for the final covariate model are shown in Figure **8** and pcVPC plots are shown in Figure ***9***.

- Age is a predictor of peripheral volume (V3). The difference in exposures related to age is ≤5% in C_{max} or AUC_{0-24} and is not a clinically relevant covariate with respect to the magnitude of effect.

- Food (snack, standard meal, or high-fat meal) increases bioavailability (F1) and exposures C_{max} and AUC_{0-24}) by approximately 44%.

- VVC patients are estimated to have 42% larger V3 and 35% higher F1 than healthy subjects.

Table 16-33. Population Pharmacokinetic Parameter Estimates for the Final Model

Parameter	Estimate	IIV (CV%)	BS Median [95CI]
θ_1: CL (L/h)	8.02	27.1	9.85 [7.21-11.9]
θ_2: V2 (L)	48.4	21.2	59 [42.9-73]
θ_3: V3 (L)	157	2.97	193 [142-229]
θ_4: Q3 (L/h)	15.3		18.8 [13.4-22.7]
θ_5: K14 (1/h)	0.214 (fixed)		0.214 (fixed)
θ_6: F1	0.159	26.8	0.195 [0.141-0.233]
θ_7: SD Additive Error [Single Dose, Ph1]	2.63		2.58 [1.13-3.66]
θ_8: SD Proportional Error [Single Dose, Ph1]	0.293		0.289 [0.257-0.325]
θ_9: ALAG1 (h)	0.140 (fixed)		0.140 (fixed)
θ_{10}: ΔF1 from fasted [Snack, std. meal, or high-fat meal]	0.444		0.444 [0.255-0.7]
θ_{11}: SD Additive Error [Multiple Dose, Ph1]	11.2		10.3 [4.78-31]
θ_{12}: SD Proportional Error [Multiple Dose, Ph1]	0.205		0.195 [0.148-0.254]
θ_{13}: K42 (1/h)	1.75 (fixed)	85.0	1.75 (fixed)
θ_{14}: Age~V3	0.375		0.379 [0.241-0.536]
θ_{15}: ΔK42 from total daily dose>30	-0.762		-0.762 [-0.855- -0.563]
θ_{16}: SD Additive Error [Ph2]	3.97		3.61 [0.217-6.13]
θ_{17}: SD Proportional Error [Ph2]	0.0615		0.0603 [0.0422-0.0925]
θ_{18}: ΔV3 from healthy subjects [VVC patients]	0.417		0.416 [0.204-0.662]
θ_{19}: ΔCL for 150 mg BID	1.09		1.04 [0.376-1.99]
θ_{21}: ΔF1 from total daily dose≤600 mg [total daily dose>600 mg]	-0.348		-0.344 [-0.466- -0.178]

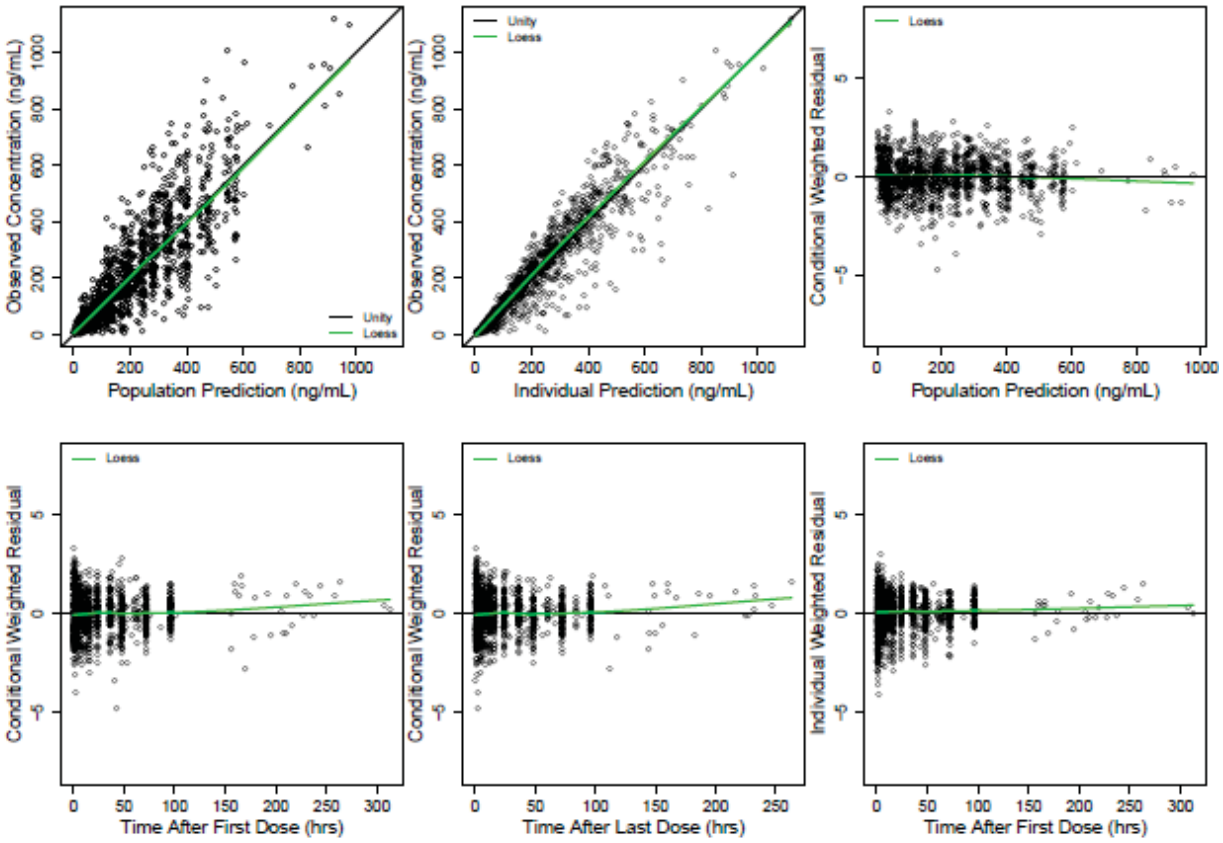
θ_{22}: ΔF1 from healthy subjects [VVC patients]	0.350		0.341 [0.0877-0.601]

Parameter	Estimate	Shrinkage (%)	BS Median [95CI]
Variance of $\eta_{1:}$ CL	0.0737	10.6	0.0631 [0.0356-0.135]
Variance of $\eta_{2:}$ V2	0.0450 (fixed)	63.8	0.0450 (fixed)
Variance of η_3: V3	8.84E-04 (fixed)	87.4	8.84E-04 (fixed)
Variance of η_6: F1	0.0717	15.0	0.0642 [0.0354-0.156]
Variance of η_8: K42	0.723	26.9	0.712 [0.385-1.14]

Abbreviations: Covariate ~ PK Parameter = effect of covariate on the PK parameter, ϑ = fixed effect, η = between subject variability, IIV = inter-individual variability, Δ = change, CL = central clearance, V2 = central volume, V3 = volume of peripheral compartment, Q3 = inter-compartmental clearances between central compartment and peripheral compartment, K14 = rate from depot to transit compartment, K42 = rate from transit compartment to central compartment, F1 = Fraction absorbed by compartment 1, SD = standard deviation, CV% = coefficient of variation, L = liters, h = hours, CI = confidence interval, BS = bootstrap, VVC = vulvovaginal candidiasis.

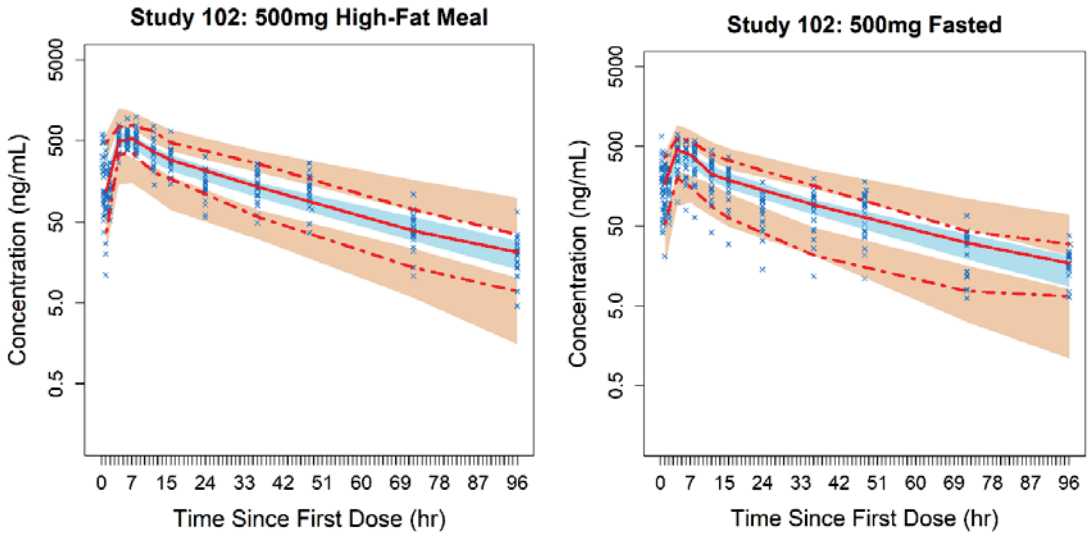
Source: Applicant's scy-078-pop-pk-003 Report, Table-12-2 on Page 31 (link).

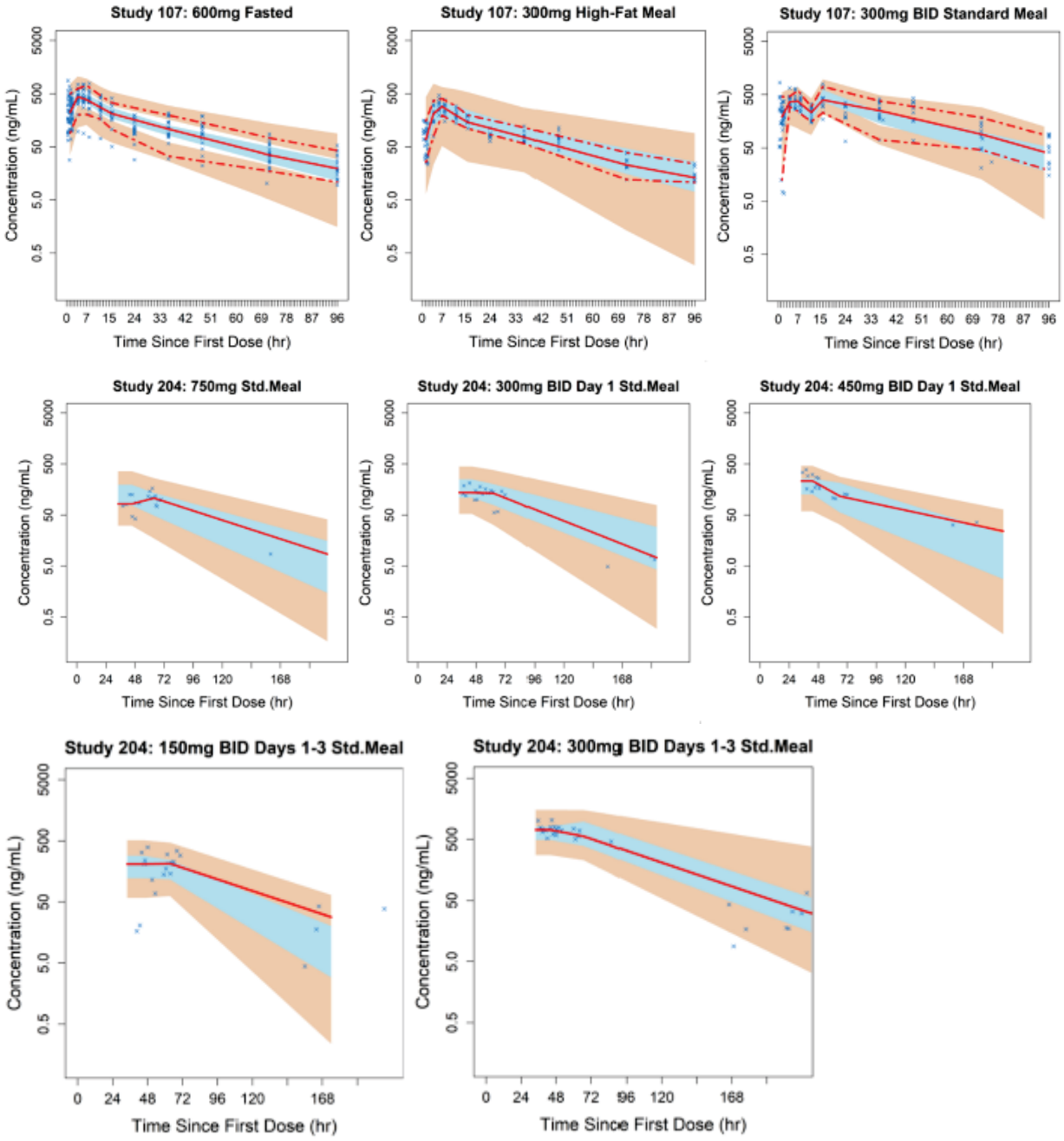
Figure 8. Goodness-of-fit plots for final covariate model



Source: Applicant's scy-078-pop-pk-003 Report, , Figure 12-3-2 on Page 33 (link).

Figure *9*. pcVPC plots for final covariate model





Source: Applicant's scy-078-pop-pk-003 Report, Figure 12-3 on Page 34 (link).

Simulation based on final model

The final population PK model was used to simulate PK profiles for dosing scenarios, one day 150 mg BID, 300 mg BID, and 600 mg BID dosing in VVC patients as fasted or fed, exposures (Cmax, AUC0-24), summarized Table 16-34, which has similar simulation results on AUC_{0_24} and Cmax mean values as those of the reviewer.

Table 16-34. Summary of exposures (Cmax, AUC0-24) from simulation of VVC patients receiving 150 mg BID, 300 mg BID, and 600 mg BID of ibrexafungerp

Fasted/Fed Status	Treatment	AUC_{0-24} (ng.h/mL)				C_{max} (ng/mL)			
		5th	Mean	Median	95th	5th	Mean	Median	95th
Fasted	150mg BID	1237	2113	2192	2666	82	136	137	181
	300mg BID	5002	6832	6871	8440	313	435	441	534
	600mg BID	6526	8914	8965	11011	409	568	575	697
Fed	150mg BID	1786	3052	3166	3850	119	196	198	262
	300mg BID	7224	9867	9923	12188	453	629	636	771
	600mg BID	9425	12873	12947	15902	591	821	830	1006

Source: Applicant's scy-078-pop-pk-003 Report, Table-1-4 on Page 6 (link).

16.5. Clinical Safety Appendix

This appendix contains additional data supporting Section 8.2.4 Safety Results.

Serious Adverse Events

Table 16-35 Serious Adverse Events – Pooled Phase 1 Trials

	Multiple Dose (N=169) n (%)	Placebo + Multiple Dose (N=16) n (%)	Placebo + Single Dose (N=16) n (%)	Single Dose (N=97) n (%)	Total (N=298) n (%)
Any SAE	1 (0.6)	0	0	2 (2.0)	3 (1.0)
System Organ Class **Preferred Term**					
Immune system disorders					
Type IV hypersensitivity reaction	1 (0.6)	0	0	0	1 (0.3)
Investigations					
Hepatic enzyme increased	0	0	0	1 (1.0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Metastatic carcinoid tumour	0	0	0	1 (1.0)	1 (0.3)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Dropouts and/or Discontinuations Due to Adverse Effects

Table 16-36 Study Discontinuations Due to Adverse Events – Phase 2 Trial SCY-078-204

	Fluconazole 150 mg QD on Day 1 only (N=32) n (%)	SCY-078 150 mg BID on Days 1 to 3 (N=31) n (%)	SCY-078 300 mg BID on Day 1 only (N=30) n (%)	SCY-078 300 mg BID on Days 1 to 3 (N=32) n (%)	SCY-078 450 mg BID on Day 1 only (N=28) n (%)	SCY-078 750 mg QD on Day 1 only (N=32) n (%)	Total (N=185) n (%)
Study Discontinuations							
Study Discontinued	4 (12.5)	3 (9.7)	3 (10.0)	5 (15.6)	6 (21.4)	4 (12.5)	25 (13.5)
Reason for study discontinuation							
Withdrawal by subject	0	0	2 (6.7)	3 (9.4)	1 (3.6)	1 (3.1)	7 (3.8)
Lack of efficacy	1 (3.1)	1 (3.2)	0	2 (6.2)	2 (7.1)	0	6 (3.2)
Other	0	1 (3.2)	1 (3.3)	0	2 (7.1)	0	4 (2.2)
Physician decision	2 (6.2)	1 (3.2)	0	0	0	1 (3.1)	4 (2.2)
Adverse event[1]	0	0	0	0	0	2 (6.2)	2 (1.1)
Lost to follow-up	1 (3.1)	0	0	0	1 (3.6)	0	2 (1.1)

[1]Adverse events leading to study discontinuation were gastrointestinal events in both subjects and dizziness in one of the subjects
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Table 16-37 Study Discontinuations Due to Adverse Events – Pooled Phase 1 Trials

	Oral Ibrexafungerp Multiple Dose (N=169) n (%)	Placebo + Multiple Dose (N=16) n (%)	Placebo + Single Dose (N=16) n (%)	Oral Ibrexafungerp Single Dose (N=97) n (%)	Total (N=298) n (%)
Any TEAE Leading to Study Discontinuation[1]	5 (3.0)	0	0	3 (3.1)	8 (2.7)
System Organ Class Preferred Term					
Gastrointestinal disorders					
Abdominal pain	1 (0.6)	0	0	0	1 (0.3)
Diarrhoea	1 (0.6)	0	0	0	1 (0.3)
Nausea	1 (0.6)	0	0	0	1 (0.3)
Vomiting	1 (0.6)	0	0	0	1 (0.3)
Investigations					
Hepatic enzyme increased[2]	0	0	0	2 (2.1)	2 (0.7)

	Oral Ibrexafungerp Multiple Dose (N=169) n (%)	Placebo + Multiple Dose (N=16) n (%)	Placebo + Single Dose (N=16) n (%)	Oral Ibrexafungerp Single Dose (N=97) n (%)	Total (N=298) n (%)
General disorders and administration site conditions					
Malaise	1 (0.6)	0	0	0	1 (0.3)
Immune system disorders					
Type IV hypersensitivity reaction[3]	1 (0.6)	0	0	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Metastatic carcinoid tumour	0	0	0	1 (1.0)	1 (0.3)

[1]One additional subject discontinued the study due to identification of 2nd degree AV block after a single dose of pravastatin in a DDI study but was not included in the table because ibrexafungerp was not administered.
[2]Preferred terms "alanine aminotransferase increased" and "aspartate aminotransferase increased" were combined by the reviewer into the term "hepatic enzyme increased" for 1 subject. Both subjects with hepatic enzyme increases resulting in study discontinuation received a single 500 mg oral ibrexafungerp dose; the event was reported as an SAE in 1 subject.
[3]The type IV hypersensitivity reaction occurred in a subject receiving oral ibrexafungerp 750 mg BID x 2 days followed by 750 mg daily x 2 days; the event was an SAE.
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Significant Adverse Events

Table 16-38 Overview of Treatment-Emergent Adverse Events – Phase 2 Trials

	SCY-078-203				SCY-078-204						
	Fluconazole 150 mg QD on Day 1 only (N=32) n (%)	SCY-078 1250 mg Day 1 then 750 mg QD (3 doses) (N=32) n (%)	SCY-078 1250 mg Day 1 then 750 mg QD (5 doses) (N=32) n (%)	Total (N=96) n (%)	Fluconazole 150 mg QD on Day 1 only (N=32) n (%)	SCY-078 150 mg BID on Days 1 to 3 (N=31) n (%)	SCY-078 300 mg BID on Day 1 only (N=30) n (%)	SCY-078 300 mg BID on Days 1 to 3 (N=32) n (%)	SCY-078 450 mg BID on Day 1 only (N=28) n (%))	SCY-078 750 mg QD on Day 1 only (N=32) n (%))	Total (N=185) n (%)
Any TEAE	4 (12.5)	28 (87.5)	29 (90.6)	61 (63.5)	16 (50.0)	17 (54.8)	17 (56.7)	19 (59.4)	20 (71.4)	26 (81.2)	115 (62.2)
Any SAE	0	0	0	0	0	0	0	0	0	0	0
TEAEs leading to change in study treatment	0	0	0	0	0	0	0	0	0	2 (6.2)	2 (1.1)
Drug interrupted	0	0	0	0	0	0	0	0	0	0	0
Drug withdrawn	0	0	0	0	0	0	0	0	0	2 (6.2)	2 (1.1)
TEAEs leading to study discontinuation	0	0	0	0	0	0	0	0	0	0	0
TEAE severity											
Mild	3 (9.4)	24 (75.0)	23 (71.9)	50 (52.1)	15 (46.9)	13 (41.9)	14 (46.7)	18 (56.2)	17 (60.7)	24 (75.0)	101 (54.6)
Moderate	1 (3.1)	9 (28.1)	10 (31.2)	20 (20.8)	6 (18.8)	8 (25.8)	8 (26.7)	4 (12.5)	4 (14.3)	7 (21.9)	37 (20.0)
Severe	0	0	0	0	1 (3.1)	3 (9.7)	1 (3.3)	0	1 (3.6)	3 (9.4)	9 (4.9)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Table 16-39 Overview of Treatment-Emergent Adverse Events – Pooled Phase 1

	Multiple Dose (N=169) n(%)	Placebo + Multiple Dose (N=16) n(%)	Placebo + Single Dose (N=16) n(%)	Single Dose (N=97) n(%)	Total (N=298) n(%)
Any TEAE	127 (75.1)	11 (68.8)	13 (81.2)	46 (47.4)	197 (66.1)
Any SAE	1 (0.6)	0	0	2 (2.1)	3 (1.0)
TEAEs leading to change in study treatment					
Drug interrupted	0	0	0	0	0
Drug withdrawn	4 (2.4)	0	0	1 (1.0)	5 (1.7)
TEAE Leading to Study Discontinuation	5 (3.0)	0	0	3 (3.1)	8 (2.7)
TEAE severity					
Mild	120 (71.0)	11 (68.8)	13 (81.2)	45 (46.4)	189 (63.4)
Moderate	42 (24.9)	1 (6.2)	6 (37.5)	6 (6.2)	55 (18.5)
Severe	1 (0.6)	0	1 (6.2)	2 (2.1)	4 (1.3)
Missing data	12 (7.1)	0	5 (31.2)	2 (2.1)	19 (6.4)

Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Treatment Emergent Adverse Events and Adverse Reactions

Table 16-40 TEAE by Severity and Duration – Pooled Phase 3 Trials

	Oral ibrexafungerp 300mg BID (N=536 events) n(%)	Placebo BID (N=208 events) n(%)	Total (N=744 events) n(%)
Adverse Event Severity			
Mild	418 (78.0)	153 (73.6)	571 (76.7)
Moderate	112 (20.9)	44 (21.2)	156 (21.0)
Severe	6 (1.1)	11 (5.3)	17 (2.3%)
Adverse Event Duration			
1 day or less	228 (42.5)	93 (44.7)	321 (43.1)
2-3 days	171 (31.9)	46 (22.1)	217 (29.2)
>3 days	137 (25.6)	69 (33.2)	206 (27.7)

Source: Clinical reviewer, JMP version 15

Table 16-41 Gastrointestinal TEAE by Severity and Duration – Pooled Phase 3 Trials

	Oral ibrexafungerp 300mg BID (N=269 events)	Placebo BID (N=50 events)	Total (N=319 events)

	n(%)	n(%)	n(%)
Gastrointestinal Adverse Event Severity			
Mild	219 (81.4)	40 (80.0)	259 (81.2)
Moderate	48 (17.8)	8 (16.0)	56 (17.6)
Severe	2 (0.7)	2 (4.0)	4 (1.3)
Gastrointestinal Adverse Event Duration			
1 day or less	228 (42.5)	93 (44.7)	321 (43.1)
2-3 days	171 (31.9)	46 (22.1)	217 (29.2)
>3 days	137 (25.6)	69 (33.2)	206 (27.7)

Source: Clinical reviewer, JMP v15

Table 16-42 TEAE Occurring in ≥2% Subjects – SCY-078-203 Proof-of-Concept Trial

	Fluconazole (N=32) n(%)	SCY-078 (3 doses)[1] (N=32) n(%)	SCY-078 (5 doses)[1] (N=32) n(%)	Total (N=96) n(%)
TEAE by SOC and PT				
Gastrointestinal disorders				
Diarrhoea	1 (3.1)	20 (62.5)	25 (78.1)	46 (47.9)
Nausea	0	14 (43.8)	13 (40.6)	27 (28.1)
Vomiting	0	12 (37.5)	8 (25.0)	20 (20.8)
Abdominal pain[2]	0	11 (34.4)	8 (25.0)	19 (19.8)
Flatulence	0	1 (3.1)	1 (3.1)	2 (2.1)
Nervous system disorders				
Dizziness	0	7 (21.9)	4 (12.5)	11 (11.5)
Headache	1 (3.1)	1 (3.1)	4 (12.5)	6 (6.2)
Somnolence	1 (3.1)	1 (3.1)	0	2 (2.1)
General disorders and administration site conditions				
Fatigue[3]	1 (3.1)	1 (3.1)	1 (3.1)	3 (3.1)
Infections and infestations				
Nasopharyngitis	0	2 (6.2)	0	2 (2.1)
Musculoskeletal and connective tissue disorders				
Myalgia	1 (3.1)	0	1 (3.1)	2 (2.1)

[1] Subjects received 1250 mg loading dose then 750 mg daily for a total of 3 doses or 5 doses
[2] Includes the terms “abdominal pain” and “abdominal pain upper”
[3] Includes the terms “fatigue” and “asthenia”
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Table 16-43 TEAE Occurring in ≥2% Subjects – SCY-078-204 Dose-Finding Trial

	Fluconazole 150 mg QD on Day 1 only (N=32) n(%)	SCY-078 150 mg BID on Days 1 to 3 (N=32) n(%)	SCY-078 300 mg BID on Day 1 only (N=30) n(%)	SCY-078 300 mg BID on Days 1 to 3 (N=32) n(%)	SCY-078 450 mg BID on Day 1 only (N=28) n(%)	SCY-078 750 mg QD on Day 1 only (N=32) n(%)	Total (N=186) n(%)
Gastrointestinal disorders							
Diarrhoea	1 (3.1)	4 (12.5)	5 (16.7)	13 (40.6)	6 (21.4)	15 (46.9)	44 (23.7)
Abdominal pain [1]	5 (15.6)	5 (15.6)	2 (6.7)	4 (12.5)	5 (17.9)	7 (21.9)	28 (15.1)
Nausea	2 (6.2)	6 (18.8)	3 (10.0)	6 (18.8)	8 (28.6)	8 (25.0)	33 (17.7)
Vomiting	0	0	0	2 (6.2)	4 (14.3)	1 (3.1)	7 (3.8)
Dry mouth	2 (6.2)	1 (3.1)	1 (3.3)	0	0	0	4 (2.2)
Flatulence	0	1 (3.1)	1 (3.3)	1 (3.1)	1 (3.6)	0	4 (2.2)
General disorders and administration site conditions							
Fatigue	2 (6.2)	2 (6.2)	1 (3.3)	1 (3.1)	0	0	6 (3.2)
Infections and infestations							
Nasopharyngitis	0	1 (3.1)	2 (6.7)	1 (3.1)	0	0	4 (2.2)
Investigations							
Blood creatine phosphokinase increased	1 (3.1)	2 (6.2)	1 (3.3)	0	0	2 (6.2)	6 (3.2)
Hepatic enzyme increased[2]	1 (3.1)	2 (6.2)	1 (3.3)	0	1 (3.6)	0	5 (2.7)
Nervous system disorders							
Headache	2 (6.2)	9 (28.1)	3 (10.0)	4 (12.5)	3 (10.7)	3 (9.4)	24 (12.9)
Dizziness	0	3 (9.4)	2 (6.7)	1 (3.1)	2 (7.1)	1 (3.1)	9 (4.8)
Reproductive system and breast disorders							
Vaginal discharge	0	1 (3.1)	1 (3.3)	0	2 (7.1)	1 (3.1)	5 (2.7)

[1] Includes the terms "abdominal pain," "abdominal pain upper," "abdominal pain lower," and "abdominal discomfort."
[2] Includes the terms "hepatic enzyme increased" and " liver function test increased"
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

Table 16-44 TEAE Occurring in ≥2% Subjects – Pooled Phase 1 Trials

	Multiple Dose (N=169) n (%)	Placebo + Multiple Dose (N=16) n (%)	Placebo + Single Dose (N=16) n (%)	Single Dose (N=97) n (%)	Total (N=298) n (%)
Gastrointestinal disorders					
Diarrhoea	88 (52.1)	7 (43.8)	3 (18.8)	24 (24.7)	122 (40.9)
Abdominal pain[1]	53 (31.4)	7 (43.8)	4 (25.0)	11 (11.3)	75 (25.2)
Nausea	41 (24.3)	2 (12.5)	2 (12.5)	13 (13.4)	58 (19.5)
Vomiting	19 (11.2)	0	1 (6.2)	1 (1.0)	21 (7.0)
Abdominal distension	7 (4.1)	1 (6.2)	0	1 (1.0)	9 (3.0)
Flatulence	5 (3.0)	2 (12.5)	0	1 (1.0)	8 (2.7)
Constipation	5 (3.0)	0	0	2 (2.1)	7 (2.3)
Nervous system disorders					
Headache	32 (18.9)	3 (18.8)	4 (25.0)	10 (10.3)	49 (16.4)
Dizziness[2]	10 (5.9)	1 (6.2)	0	3 (3.1)	14 (4.7)
General disorders and administration site conditions					
Fatigue[3]	8 (4.7)	1 (6.2)	2 (12.5)	0	11 (3.7)
Infections and infestations					
Nasopharyngitis	3 (1.8)	0	5 (31.2)	1 (1.0)	9 (3.0)
Upper respiratory tract infection	7 (4.1)	0	0	0	7 (2.3)
Injury, poisoning and procedural complications					
Vascular access site pain	9 (5.3)	0	0	0	9 (3.0)
Investigations					
Orthostatic heart rate response increased	6 (3.6)	0	0	0	6 (2.0)
Metabolism and nutrition disorders					
Decreased appetite	5 (3.0)	1 (6.2)	0	0	6 (2.0)
Musculoskeletal and connective tissue disorders					
Myalgia	3 (1.8)	1 (6.2)	1 (6.2)	1 (1.0)	6 (2.0)

[1] Includes the terms “abdominal pain,” “abdominal pain upper,” “abdominal pain lower,” “abdominal discomfort,” “epigastric discomfort,” and “gastrointestinal pain”
[2] Includes the terms “dizziness” and “postural dizziness”
[3] Includes the terms “fatigue” and “asthenia”
Source: Clinical reviewer, OCS Analysis Studio version 1.4.2

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