

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211288Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215888
Priority or standard	Priority
Submit date	5/27/2021
Received date	5/27/2021
PDUFA goal date	4/27/2022
Division/office	Division of Anti-Infectives (DAI)
Review completion date	4/25/2022
Established/proper name	Oteseconazole
(Proposed) proprietary name	Vivjoa
Pharmacologic class	Azole antifungal
Code name	VT-1161
Applicant	Mycovia Pharmaceuticals, Inc.
Dosage form/formulation	Capsule
Applicant proposed indication/ population	(b) (4)
Proposed SNOMED indication	SCTID: 708126004
Regulatory action	Approval
Approved dosage	VIVJOA-only dosage regimen: - On Day 1: Administer VIVJOA 600 mg (as a single dose), then - On Day 2: Administer VIVJOA 450 mg (as a single dose), then - Beginning on Day 14: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 2 through 12). Fluconazole/VIVJOA dosage regimen: - On Day 1, Day 4, and Day 7: Administer fluconazole 150 mg orally , then - On Days 14 through 20: Administer VIVJOA 150 mg once daily for 7 days, then - Beginning on Day 28: Administer VIVJOA 150 mg once a week (every 7 days) for 11 weeks (Weeks 4 through 14).
Approved indication/ population	To reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential
Approved SNOMED term for indication	Recurrent candidiasis of vagina

Table of Contents

Table of Tables	vi
Table of Figures	xiii
Glossary	1
I. Executive Summary.....	3
1. Summary of Regulatory Action	3
2. Benefit-Risk Assessment.....	5
2.1. Benefit-Risk Framework	5
2.2. Conclusions Regarding Benefit-Risk	10
II. Interdisciplinary Assessment.....	11
3. Introduction	11
3.1. Review Issue List.....	12
3.1.1. Key Review Issues Relevant to Evaluation of Benefit	12
3.1.1.1. Assessment of the Use of VVC Medication on the Interpretation of the Efficacy of Oteseconazole	12
3.1.1.2. (b) (4)	(b) (4)
(b) (4)	(b) (4)
3.1.1.3. Support for Proposed Indications	12
3.1.2. Key Review Issues Relevant to Evaluation of Risk.....	12
3.1.2.1. Nonclinical Ocular Findings and Implications for Labeling	12
3.1.2.2. CPK Elevations	12
3.2. Approach to the Review	12
4. Patient Experience Data	18
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology	19
5.1. Nonclinical Assessment of Potential Effectiveness.....	22
6. Assessment of Effectiveness	23
6.1. Dose and Dose Responsiveness.....	23
6.2. Clinical Trials Intended to Demonstrate Efficacy	26
6.2.1. Trial CL-011.....	26
6.2.1.1. Design, Trial CL-011.....	26
6.2.1.2. Eligibility Criteria, Trial CL-011	26
6.2.1.3. Statistical Analysis Plan, Trial CL-011	27
6.2.1.4. Results of Analyses, Trial CL-011	29
6.2.2. Trial CL-012.....	34
6.2.2.1. Design, Trial CL-012.....	34
6.2.2.2. Eligibility Criteria, Trial CL-012	34
6.2.2.3. Statistical Analysis Plan, Trial CL-012	34
6.2.2.4. Results of Analyses, Trial CL-012	34

6.2.3. Trial CL-017.....	39
6.2.3.1. Design, Trial CL-017.....	39
6.2.3.2. Eligibility Criteria, Trial CL-017	40
6.2.3.3. Statistical Analysis Plan, Trial CL-017	41
6.2.3.4. Results of Analyses, Trial CL-017	43
6.3. Key Review Issues Relevant to Evaluation of Benefit.....	49
6.3.1. Assessment of the Use of VVC Medication on the Interpretation of the Efficacy of Oteseconazole	49
6.3.2. (b) (4)	(b) (4)
(b) (4)	(b) (4)
6.3.3. Support for Proposed Indications.....	57
7. Risk and Risk Management.....	58
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	58
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	60
7.3. Potential Safety Concerns Identified Through Postmarket Experience	60
7.4. FDA Approach to the Safety Review	60
7.5. Adequacy of Clinical Safety Database	60
7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database.....	63
7.6.1. Overall Adverse Event Summaries	63
7.6.2. Deaths.....	69
7.6.3. Nonfatal Serious Adverse Events.....	70
7.6.4. Dropouts and/or Discontinuations Due to Adverse Events.....	73
7.6.5. Treatment-Emergent Adverse Events	76
7.6.6. Laboratory Findings	79
7.6.7. Additional Safety Analyses.....	92
7.6.7.1. Adverse Events of Special Interest.....	92
7.6.7.2. Summary of Safety Findings From Other Studies	96
7.6.7.3. 120 Day Safety Update.....	99
7.7. Key Review Issues Relevant to Evaluation of Risk	100
7.7.1. Nonclinical Ocular Findings and Implications for Labeling	100
7.7.2. CPK Elevations	101
8. Therapeutic Individualization Therapeutic Individualization	103
8.1. Intrinsic Factors	103
8.2. Extrinsic Factors	105
8.2.1. Food Effect.....	105
8.2.2. Drug Interactions.....	105
8.3. Plans for Pediatric Drug Development	107

8.4. Pregnancy and Lactation.....	108
9. Product Quality	110
9.1. Device or Combination Product Considerations	111
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure	111
11. Advisory Committee Summary.....	113
III. Appendices.....	114
12. Summary of Regulatory History	114
13. Pharmacology Toxicology: Additional Information and Assessment	116
13.1. Summary Review of Studies Submitted Under the IND	116
13.1.1. Primary Pharmacology.....	116
13.1.2. Secondary Pharmacology.....	117
13.1.3. Safety Pharmacology	119
13.1.4. General Toxicology.....	119
13.1.5. Pharmacokinetics	123
13.1.6. Genetic Toxicology.....	126
13.1.7. Reproductive Toxicology.....	126
13.2. Individual Reviews of Studies Submitted to the NDA.....	136
13.2.1. Carcinogenicity	136
13.2.2. General Toxicology; Additional Studies.....	139
13.2.3. Reproductive Toxicology: Additional Studies.....	140
14. Clinical Pharmacology: Additional Information and Assessment	152
14.1. In Vitro Studies.....	152
14.1.1. Plasma Protein Binding (MC11M-0008.1 and OPR-VMT-0449.01).....	152
14.2. In Vivo Studies	157
14.2.1. In Vivo Activity in an Estrogen-Dependent Murine Model of Vaginal Candidiasis.....	157
14.2.1.1. Human PK Studies in Healthy Volunteers	160
14.3. Pharmacometrics Review	184
14.3.1. Applicant’s Population PK Analysis.....	184
14.3.2. Reviewer’s Assessment of the Population PK Analysis	198
14.3.3. Appendix	204
14.4. Summary of Bioanalytical Method Validation and Performance.....	204
15. Trial Design: Additional Information and Assessment.....	206
15.1. Trial CL-011 Trial Design Synopsis.....	206
15.2. Trial CL-017 Trial Design Synopsis.....	219
16. Efficacy: Additional Information and Assessment	232
16.1. Additional Analyses for Study CL-011	232
16.2. Additional Analyses for Study CL-012	236

16.3. Additional Analyses for Study CL-017	241
16.4. Additional Analyses for Studies CL-011, CL-012 and CL-017	245
16.5. Trial CL-006 Trial Design	248
17. Clinical Safety: Additional Information and Assessment	255
17.1. Nonfatal Treatment-Emergent SAEs Narratives	260
17.1.1. Trial CL-011 Nonfatal Treatment-Emergent SAEs	260
17.1.2. Trial CL-012 Nonfatal Treatment-Emergent SAEs	263
17.1.3. Trial CL-017 Nonfatal Treatment-Emergent SAEs	269
17.1.4. Trial CL-006 Nonfatal Treatment-Emergent SAEs	272
17.2. TEAEs Leading to Discontinuation of Study Drug	276
17.2.1. Trial CL-011 TEAEs Leading to Discontinuation of Study Drug	276
17.2.2. Trial CL-012 TEAEs Leading to Discontinuation of Study Drug	277
17.2.3. Trial CL-017 TEAEs Leading to Discontinuation of Study Drug	278
17.2.4. Trial CL-006 TEAEs Leading to Discontinuation of Study Drug	279
17.3. Adverse Events of Special Interest--Narratives	279
17.3.1. Hepatotoxicity	279
17.3.2. Medical Dictionary for Regulatory Activities-Based Adverse Event Diagnostics Related Hepatic Function Elevations Narratives	292
17.3.3. Drug Allergy/Hypersensitivity/Anaphylactic Reactions.....	297
17.4. Creatine Phosphokinase Narratives	304
17.4.1. CPK Elevations-Trial CL-011.....	304
17.4.2. CPK Elevations-CL-012	308
17.4.3. CPK Elevations-CL-017	310
17.4.4. CPK Elevations-CL-006	312
17.5. Phase 2/3 Pregnancy Summary Listings.....	319
18. Mechanism of Action/Drug Resistance: Additional Information and Assessment.....	321
19. Other Drug Development Considerations: Additional Information and Assessment.....	322
20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)	323
21. Labeling Summary of Considerations and Key Additional Information	323
22. Postmarketing Requirements and Commitments	327
23. Financial Disclosure	328
24. References	330
25. Review Team.....	332

Table of Tables

Table 1. Administrative Application Information	i
Table 2. Benefit-Risk Framework.....	5
Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations.....	13
Table 4. Patient Experience Data Submitted or Considered.....	18
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics.....	19
Table 6. A Comparison of MIC Values From Isolates for Three Phase 3 Studies.....	23
Table 7. Oteseconazole Minimum Plasma Concentrations Observed in Phase 2b and Phase 3 Trials.....	25
Table 8. Subjects Screened and Randomized, Trial CL-011	29
Table 9. Subject Disposition, Trial CL-011: ITT Population	30
Table 10. Demographics and Baseline Characteristics, Trial CL-011: ITT Population....	30
Table 11. Trial CL-011 Baseline Signs and Symptoms and Microbiologic Characteristics, ITT Population	31
Table 12. Proportion of Subjects ≥ 1 Culture-Verified Acute VVC Episodes During Maintenance Phase (by Week 48) for Trial CL-011: ITT Population	33
Table 13. Time to First Recurrence of a Culture-Verified Acute VVC Episode Through Week 48 for Trial CL-011: ITT Population.....	33
Table 14. Subjects' Screening and Randomization, Trial CL-012	35
Table 15. Patient Disposition, Trial CL-012.....	35
Table 16. Demographic and Baseline Characteristics for Trial CL-012: ITT Population	36
Table 17. Trial CL-012 Baseline Microbiologic Characteristics, ITT Population	37
Table 18. Proportion of Subjects ≥ 1 Culture-Verified Acute VVC Episodes During Maintenance Phase for Trial CL-012: ITT Population.....	38
Table 19. Time to First Recurrence of a Culture-Verified Acute VVC Episode for Trial CL-012: ITT Population.....	38
Table 20. Subjects' Screening and Randomization, Trial CL-017	43
Table 21. Subject Disposition, Trial CL-017.....	44
Table 22. Subjects' Demographic and Baseline Characteristics for Trial CL-017: ITT Population	44
Table 23. Trial CL-017 Baseline Signs/Symptoms and Microbiologic Characteristics, ITT Population	45
Table 24. Proportion of Subjects Who Failed Induction or Who had ≥ 1 Culture- Verified Acute VVC Episodes During Postrandomization Through Week 50 for Trial CL-017: ITT Population.....	46
Table 25. Proportion of Subjects With Resolved Acute VVC Infections at Day 14 for Trial CL-017: ITT Population.....	47

Table 26. Proportion of Subjects With Clinical Cure at Day 14 for Trial CL-017: Induction mITT Population.....	48
Table 27. Time to First Recurrence of a Culture-Verified Acute VVC Episode For Trial CL-017 :ITT Population.....	48
Table 28. Culture-Verified Acute VVC Recurrence and Receipt of VVC Medication During Maintenance (ITT Population), Trials CL-011 and CL-012	50
Table 29. Recurrence Based on KOH Positive Acute VVC During Maintenance ITT Population Trials CL-011 and CL-012	51
Table 30. Number of Times Treated With a VVC Medication During Maintenance (ITT Population), Trials CL-011 and CL-012	52
Table 31. Resolution at Day 14 and Recurrence Based on Culture Verified Acute VVC and Receipt of VVC Medication During Maintenance ITT Population Trial CL-017	52
Table 32. Failure to Resolve at Day 14 or Recurrence Based on KOH Positive Acute VVC During Maintenance ITT Population Trials CL-017.....	53
Table 33. Number of Times Treated With a VVC Medication During Maintenance Phase ITT Population Trial CL-017	53
Table 34. Fluconazole and Placebo Clinical Response Rates.....	55
Table 35. Duration of Exposure, Safety Population, Trials 011, 012, 017 and 006 (ISS)	62
Table 36. Overview of Treatment-Emergent Adverse Events, Safety Population, Trials 011, 012, and 017 (ISS)	65
Table 37. Overview of Treatment-Emergent Adverse Events, Safety Population, Trials 006 (ISS).....	68
Table 38. Serious Adverse Events by System Organ Class and Preferred Term, Pooled Phase 3 Safety Population, Trials CL-011, -012, and -017 (ISS).....	71
Table 39. Nonfatal, Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Supportive Phase 2 Trial 006 (ISS Population).....	73
Table 40. Treatment-Emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Pooled Phase 3 Safety Population, Trials CL-011, -012, and -017 (ISS).....	75
Table 41. Treatment-Emergent Adverse Events Occurring at $\geq 1\%$ Frequency in Pooled Oteseconazole Treatment Group by System Organ Class and Preferred Term/Grouped Query, Safety Population, Trials 011, 012 and 017 (ISS).....	77
Table 42. Patients With One or More Hematology Analyte Values Outside Specified Levels, Safety Population, Trials CL-017, -012, -011	80
Table 43. Electrolyte/Chemistry Findings in the Phase 3 Trials	82
Table 44. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Phase 3 Trials 011, 012, 017 (ISS)	84

Table 45. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Post-Baseline Laboratory Toxicities, Safety Population, Phase 2b Trial 006 (ISS).....	85
Table 46. Alanine Aminotransferase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS) ...	87
Table 47. Aspartate Aminotransferase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS)	88
Table 48. Alkaline Phosphatase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS) ...	89
Table 49. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Post-Baseline Laboratory Toxicities, Safety Population, Trial 006 (ISS)	91
Table 50. Patients Identified With a Case of Temple’s Corollary, Safety Population, Trials 017, 012, 011 and 006 (ISS)	93
Table 51. QTcF Interval (msec) Shifts From Baseline for Graded Maximal Post-Baseline Toxicities, Safety Population, Trials 011, 012, 017 (ISS)	94
Table 52. Percentage of Patients With Maximum Post-Baseline Absolute Change From Baseline QTcF Interval (msec), Safety Population, Trials 011, 012, 017 (ISS)	94
Table 53. Number of Animals With Specific Ophthalmology Findings on Postnatal Day 21 in Rat Pups Born to Mothers Dosed With Oteseconazole via Oral Gavage Once Daily From Gestation Day 6 Through Lactation Day 20	101
Table 54. Nonclinical Data Supporting Labeling on Pregnancy and Lactation	108
Table 55. Sterol (%) Composition in Two Strains of <i>C. albicans</i> , (SC5314 and CA14) ± VT-1161 at 0.004 µg/ml. Maximum Values Underlined.....	117
Table 56. Binding Parameters for Oteseconazole to <i>C. albicans</i> CYP51 (CaCYP51) and Human CYP51 (HuCYP51).....	117
Table 57. Oteseconazole IC ₅₀ Values With <i>C. albicans</i> CYP51 and Human CYP51	117
Table 58. In Vitro Pharmacology: Binding Assays for Select Receptors Inhibited by 10µM Oteseconazole (by Greater Than 50%)	118
Table 59. In Vitro Inhibition of Human Transporters of Oteseconazole	118
Table 60. Safety Pharmacology Studies	119
Table 61. Methods for Study 2139-002	120
Table 62. Observations and Results: Changes From Control	120
Table 63. Histopathology Findings (Number of Animals With Findings) After 26 weeks of Dosing With Oteseconazole	121
Table 64. Enzyme Induction	122
Table 65. Findings (Number Of Animals With Findings) in Recovery Animals.....	122
Table 66. Summary of 26-Week Oral Repeat-Dose Mean Plasma Oteseconazole Toxicokinetic Parameters in Rat.....	123
Table 67. Methods for Study 2130-001	124

Table 68. Observations and Results for Study 2130-001	124
Table 69. Necropsy/Histopathology Findings	125
Table 70. Genetic Toxicology.....	126
Table 71. Methods of Male Fertility and Early Embryonic Development for Study 2130-009	127
Table 72. Observations and Results for Study 2130-009	128
Table 73. Methods of Fertility and Early Embryonic Development for Study 2130- 008.....	129
Table 74. Observations and Results for Study 2130-008	129
Table 75. Oral Embryo-Fetal Development Study Design.....	130
Table 76. Rat Oral Embryo-Fetal Study Findings	131
Table 77. Toxicokinetics Estimated for Embryo-Fetal Development Study in Rats.....	131
Table 78. Methods of Oral Embryo-Fetal Developmental Study in Rabbits.....	132
Table 79. Observations and Results for Study 2130-007	133
Table 80. Oteseconazole Pharmacokinetics in Pregnant Rabbits	133
Table 81. Methods of Oral Pre and Postnatal Developmental Study in Rats	134
Table 82. Observations and Results in Oral Pre and Postnatal Developmental Study in Rats	134
Table 83. Toxicokinetics.....	134
Table 84. Survival in F1 Pups (% per Litter).....	135
Table 85. Clinical Signs in F1 Pups.....	135
Table 86. Bodyweights in F1 Pups	135
Table 87. Summary of Pup Litter Plasma Oteseconazole Concentrations on Day 4 and Day 20.....	135
Table 88. Summary of Pup Litter Plasma Oteseconazole Concentrations for PND 35, 85, and 120.....	135
Table 89. Tumor Types With p values ≤ 0.05 for Dose-Response Relationship or the Pairwise Comparisons in a 104-Week Oral Carcinogenicity Study in Rats.....	137
Table 90. Incidence of Hemorrhage in Rats After Dosing at 5/3 mg/kg/day for 77 Weeks (Males) or 86 Weeks (Females)	137
Table 91. Summary of Effects on Reproductive Hormones Measured by Enzyme- Linked Immunosorbent Assay and LC-MS/MS	139
Table 92. Methods for Study 01234002	141
Table 93. Observations and Results for Study 01234002.....	141
Table 94. Hematology in Rat Pups on PND 24-25.....	142
Table 95. Ophthalmic Findings PND 15-18	142
Table 96. Ophthalmic Findings PND 26-30	142
Table 97. Ophthalmic Findings PND 50-55	142

Table 98. Necropsy Findings	142
Table 99. Methods of Oral Pre and Postnatal Developmental Study in Rats	143
Table 100. Observations and Results for Study 01234003.....	144
Table 101. Results for Study 01234003.....	144
Table 102. Preweaning Clinical Observations (No. of Pups [No. of Litters]).....	144
Table 103. Bodyweights on PND 10 and PND 21.....	145
Table 104. Hematology (% Change From Control) in Rat Pups Dosed With Oteseconazole	145
Table 105. Ophthalmology Findings (Number of Animals Affected) on PND 21.....	145
Table 106. Ophthalmology Findings-Postweaning (PND 34).....	145
Table 107. Summary of Gross Pathology Findings PND 21 (Non-Selected Animals)...	146
Table 108. Summary of Gross Pathology Findings PND 33-34.....	146
Table 109. Microscopic Findings PND 21	146
Table 110. Microscopic Findings PND 34	146
Table 111. Methods for Study 01234004	147
Table 112. Observations and Results for Study 01234004.....	148
Table 113. Postnatal Survival %	148
Table 114. Body Weights in F1 Pups	148
Table 115. Oteseconazole-Related Increase in Lens Opacity in Hsd:SD and CrI:WI(Han) Rat	149
Table 116. Oteseconazole-Related Hematology, Coagulation and Clinical Chemistry Findings.....	149
Table 117. Batch Analyses for GMP Batches of Oteseconazole Manufactured by (b) (4)	151
Table 118. Mechanistic Static Assessment of the Need to Conduct an In Vivo Human DDI Study – CYP Inhibition + Induction.....	154
Table 119. Oteseconazole Drug Concentrations ± SD in Plasma and Vaginal Tissue....	158
Table 120. Fluconazole and Oteseconazole MICs for Clinical Isolates Used in Study VMT-LSU-2	159
Table 121. Statistical Analyses of Mean CFU Data (P-values Based on Mann- Whitney U Test).....	160
Table 122. Mean (±SD) PK Parameters for Oteseconazole in PK Population.....	161
Table 123. Analysis of Dose Proportionality for Dose Range of 20 mg to 320 mg.....	162
Table 124. Mean (± SD) of Day 7 NCA PK Parameters	162
Table 125. Mean (± SD) Compartmental PK Parameters.....	163
Table 126. Mean Oteseconazole Plasma PK Parameters in Japanese Versus Western Subjects	164

Table 127. Comparison of Oteseconazole Plasma PK Parameters Under Fasted vs. Fed (High-Fat, High-Calorie) Conditions.....	166
Table 128. Comparison of Oteseconazole Plasma PK Parameters Under Fasted vs. Fed (Low-Fat, Low-Calorie) Conditions	166
Table 129. Oteseconazole Plasma PK Parameters for 150 mg (b) (4) Tablet Compared to the 150 mg (b) (4) Capsule Under Fed Conditions.....	166
Table 130. Mean Cumulative Recovery (% Dose) of Total Radioactivity in Urine and Feces Following a Single Oral Dose of [¹⁴ C] Oteseconazole to Healthy Female Subjects.....	168
Table 131. PK Parameters of Plasma Oteseconazole and Plasma and Whole Blood Radioactivity.....	170
Table 132. Relative Bioavailability of Midazolam in the Presence of Oteseconazole....	172
Table 133. Digoxin PK Parameters-Summary of Statistical Comparisons	173
Table 134. Rosuvastatin PK Parameters - Summary of Statistical Comparison	175
Table 135. Summary of Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone Alone on Day 1 or Coadministration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone With Multiple Doses of 150 mg VT-1161 on Day 21 (PK Population).....	176
Table 136. Summary of Statistical Comparisons of Plasma NE Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg EE/1 mg NE Alone on Day 1 or Coadministration of a Single Dose of 35 µg EE/1 mg NE With Multiple Doses of 150 mg Oteseconazole on Day 21.....	177
Table 137. Percentage of Subjects With Therapeutic Cure at TOC Visit (Day 28).....	178
Table 138. Mean PK Parameters Following Single a Dose of 300 or 600 mg Oteseconazole	179
Table 139. Percentage of Subjects With 1 of More Culture-Verified Acute VVC Infections Through Week 48 (Intent-to-Treat Population).....	180
Table 140. Summary of Oteseconazole PK by Treatment Arm	180
Table 141. Oteseconazole C _{min} (ng/mL) Presented as Mean (SD)	182
Table 142. Summary of Oteseconazole Noncompartmental Pharmacokinetic Parameters by Treatment and Day.....	183
Table 143. Logistic Regression for the Proportion of Subjects With ≥ 1 Culture-Verified Acute VVC Episodes During the Maintenance Phase.....	184
Table 144. Utility of the Population PK Model.....	184
Table 145. Oteseconazole Clinical Studies Used for the Population Pharmacokinetic Analysis.....	186
Table 146. Summary of Baseline Demographic Characteristics	191
Table 147. Parameter Estimates From the Final Population PK Model.....	195
Table 148. Bioanalytical Methods	204

Table 149. Visit Windows for Early Termination and Unscheduled Visits	219
Table 150. Trial CL-011 Screening Signs and Symptoms and Microbiologic Characteristics, ITT Population	232
Table 151. Subgroup Analyses of Primary Endpoint Trial CL-011: ITT Population	233
Table 152. Proportion of Subjects With ≥ 1 Positive Culture for <i>Candida</i> Species During the Maintenance Phase and Proportion of Subjects With ≥ 1 Culture Verified Acute VVC Episode Through Week 24 for Trial CL-011: ITT Population	235
Table 153. SF MSC and Total Score Change From Screening Through Week 48 for Trial CL-011:ITT Population.....	236
Table 154. Trial CL-012 Screening Signs and Symptoms and Microbiologic Characteristics, ITT Population	237
Table 155. Subgroup Analyses of Primary Endpoint Trial CL-012:ITT Population	238
Table 156. Proportion of Subjects With ≥ 1 Positive Culture for <i>Candida</i> Species During the Maintenance Phase and Proportion of Subjects With Culture-Verified Acute VVC Episode Through Week 24 for Trial CL-012 : ITT Population	240
Table 157. SF-36 MCS and Total Score Changes From Screening Through Week 48 for Trial CL-012: ITT Population.....	240
Table 158. Applicant’s Original Analysis of Proportion of Subjects Who Had ≥ 1 Culture-Verified Acute VVC Episodes During Post- Randomization Through Week 50 for Trial CL-017:ITT Population.....	241
Table 159. Subgroup Analysis of Primary Endpoint of Proportion of Subjects Who Failed Induction or Who Had ≥ 1 Culture-Verified Acute VVC Episodes During Post- Randomization Through Week 50 for Trial CL-017: ITT Population	242
Table 160. Proportion of Subjects With ≥ 1 Culture-Verified Acute VVC Episode During Maintenance Phase (Post Day 14 Through Week 50) for Trial CL-017: ITT Population	243
Table 161. Proportion of Subjects With Positive Culture for <i>Candida</i> Species During the Maintenance Phase (Post Day 14 Through Week 50) for Trial CL-017: ITT Population	244
Table 162. Trial CL-017 Day 14 Signs and Symptoms and Microbiologic Characteristics, ITT Population	244
Table 163. Summary of Recurrences for Trials CL-011 and CL-012	245
Table 164. Summary of Recurrences for Trial CL-017	246
Table 165. Incomplete Follow-Up in Trials CL-011, CL-012 and CL-017.....	246
Table 166. Sensitivity Analysis of Culture Verified Acute VVC Episode Excluding Subjects/Sites with Accidental Unblinding in Trials CL-011 and CL012.....	248
Table 167. Trial CL-006 Baseline Demographic Characteristics, ITT Population	250
Table 168. Percentage of Subjects With 1 or More Culture-Verified Acute VVC Infections Through Week 48 (Intent-to-Treat Population).....	254
Table 169. Baseline Demographic and Clinical Characteristics, Safety Population (Pooled Phase 3 Trials-CL-011, CL-012, CL-017)	255

Table 170. Treatment-Emergent Adverse Events Occurring at $\geq 1\%$ Frequency in Combined Oteseconazole Treatment Group by System Organ Class and Preferred Term/Grouped Query, Safety Population, Phase 2 Trial 006 (ISS).....	257
Table 171. Results for Subject CL-011 (b) (6)	282
Table 172. Results for Subject CL-011 (b) (6)	282
Table 173. Results for Subject CL-011 (b) (6)	283
Table 174. Results for Subject CL-011 (b) (6)	283
Table 175. Results for Subject CL-012 (b) (6) 5	285
Table 176. Results for Subject CL-017 (b) (6)	287
Table 177. Results for Subject CL-017 (b) (6)	287
Table 178. Results for Subject CL-006 (b) (6)	290
Table 179. Results for Subject CL-006 (b) (6)	290
Table 180. Results for Subject CL-006 (b) (6)	291
Table 181. Results from Subject CL-011 (b) (6)	294
Table 182. Results from Subject CL-011 (b) (6)	294
Table 183. Results from Subject CL-011 (b) (6)	294
Table 184. Results From Subject CL-012 (b) (6)	296
Table 185. Pregnancy Listing - Phase 2/3 RVVC Pool	319
Table 186. Covered Clinical Studies: CL-011 and CL-012.....	328
Table 187. Reviewers of Integrated Assessment	332
Table 188. Additional Reviewers of Application	333
Table 189. Signatures of Reviewers	335

Table of Figures

Figure 1. Oteseconazole PK Profiles for 2-Day (a) and 7-Day Starting Dose (b).....	25
Figure 2. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-011: ITT Population.....	34
Figure 3. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-012: ITT Population.....	39
Figure 4. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-017	49
Figure 5. Drug-Induced Liver Injury Case Screening Plot, Safety Population, Trials 017, 012, 011 and 006 (ISS)*	92
Figure 6. Analysis of Effect of Renal Function on Oteseconazole Clearance.....	104
Figure 7. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis.....	158

Figure 8. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis Following Inoculation With Isolate AR466-06 (Left) and Isolate JJ330-06 (Right)	159
Figure 9. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis Following Inoculation With Isolate AR466-06 (Left) and Isolate LP1158-07 (Right).....	160
Figure 10. Mean Oteseconazole Plasma Concentration-Time Plots (20 – 320 mg).....	161
Figure 11. Mean Oteseconazole Plasma Concentration-Time Profiles at Day 7.....	163
Figure 12. Mean Digoxin Plasma Concentrations Over Time Following the Administration of Digoxin Alone or Coadministration With Single or Multiple Doses of Oteseconazole (CL-015)	174
Figure 13. Goodness of Fit Plots From the Final PK Model	197
Figure 14. Visual Predictive Check for the Final PK Model	198
Figure 15. Predicted Oteseconazole AUC_{τ} , C_{max} , and C_{min} Under the Proposed Regimen in Adolescent and Adults With Recurrent Vulvovaginal Candidiasis, Stratified by Body Weight.	201
Figure 16. Ratio of Median Predicted Oteseconazole AUC_{τ} , C_{max} , and C_{min} Under the Proposed Regimen in Adolescent and Adults With Recurrent Vulvovaginal Candidiasis, Stratified by Body Weight.....	202

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC _{0-24h}	area under the curve from 0 to 24 hours
AUC _{0-72h}	area under the curve from 0 to 72 hours
AUC _τ	area under the concentration-time curve during the dosing interval
AUC _{0-∞}	area under the curve from zero to infinity
AUCR	area under the curve ratio
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BV	bacterial vaginosis
Ca ²⁺	calcium
CL/F	apparent clearance
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
CPK	creatine phosphokinase
Cr	creatinine
CT	computed tomography
CYP	cytochrome P450 isoenzyme
DDI	drug-drug interaction
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
ER	emergency room
ETA	interindividual random effect
FDA	Food and Drug Administration
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GLP	good laboratory practice
IC ₅₀	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	investigational new drug
IR	information request
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
K ⁺	potassium
Ka	absorption rate constant
KOH	potassium hydroxide
LC-MS/MS	liquid chromatography with tandem mass spectrometry

LD	loading dose
LLOQ	lower limit of quantification
MATE	multidrug and toxic compound extrusion
MCS	mental component score
MI	multiple imputation
MIC	minimum inhibitory concentration
MIC ₅₀	minimum inhibitory concentration to inhibit growth of 50% of organisms
MIC ₉₀	minimum inhibitory concentration to inhibit growth of 90% of organisms
mITT	modified intent-to-treat
MRHD	maximum recommended human dosage
MRI	magnetic resonance imaging
NDA	new drug application
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
OFV	objective function value
OTE	oteseconazole
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
popPK	population pharmacokinetic
PT	preferred term
Q/F	apparent intercompartmental clearance
QD	once daily
RVVC	recurrent vulvovaginal candidiasis
SAE	serious adverse event
SF-36	36 item short form survey
SOC	system organ class
T _{1/2}	half life
TEAE	treatment-emergent adverse event
T _{max}	time to maximum concentration
TOC	test of cure
ULN	upper limit of normal
URI	upper respiratory infection
UTI	urinary tract infection
V ₂ /F	apparent central volume of distribution
V ₃ /F	apparent peripheral volumes of distribution
V _z /F	apparent volume of distribution during terminal phase
VVC	vulvovaginal candidiasis
wnl	within normal limits

I. Executive Summary

1. Summary of Regulatory Action

The new drug application (NDA) 215888 for oteseconazole, an azole antifungal drug, was submitted by Mycovia Pharmaceuticals, Inc. The Applicant proposed oteseconazole (b) (4)

(b) (4)
(b) (4) The NDA was reviewed by the multidisciplinary review team.

The clinical and statistical reviewers concluded that the Applicant provided insufficient information to demonstrate the efficacy of oteseconazole (b) (4)

(b) (4) The review team also concluded that ocular abnormalities observed in pre- and postnatal developmental studies along with oteseconazole's prolonged drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) should result in contraindication of oteseconazole for pregnant and lactating females as well as females of reproductive potential. In making their risk-benefit assessments the review team also considered that RVVC is a non-life-threatening disease. Consequently, the team recommended to indicate oteseconazole to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential, and I, the signatory authority for this application, concur with those recommendations.

The Applicant submitted three adequate and well controlled phase 3 trials. The trials consisted of an induction phase to treat an acute episode of RVVC and a maintenance phase. In two trials fluconazole was used in the induction phase followed by an 11-week maintenance phase of either oteseconazole or placebo weekly. In these trials oteseconazole was superior to placebo in the proportion of patients with ≥ 1 acute VVC episode through Week 48 post-randomization.

In the third trial, during the induction phase, patients received either fluconazole or oteseconazole followed by a maintenance regimen of either oteseconazole weekly or placebo weekly for 11 weeks. Oteseconazole was superior to fluconazole/placebo in the proportion of patients with ≥ 1 acute VVC episode through Week 50 post-randomization. (b) (4)

(b) (4)

(b) (4) While the Applicant proposed (b) (4)

(b) (4)

(b) (4) their approaches are deemed unacceptable by the clinical and statistical reviewers.

The safety profile of oteseconazole in the three phase 3 clinical trials was comparable to the comparator regimens. Urinary tract infections, bacterial vaginosis, headache, nausea, abdominal pain, pyrexia and diarrhea were the most commonly observed adverse reactions.

NDA 215888
Vivjoa (oteseconazole)

The overall benefit-risk profile is described in the Benefit-Risk Framework below. For detailed information supporting the regulatory action, please refer to the clinical and statistical reviews included in this Integrated Assessment document.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 70 to 75% of all females will experience an infection with vulvovaginal candidiasis (VVC) at least once in their lifetime. Moreover, it is estimated that 40 to 50% of these females will experience a recurrence of VVC (Sobel 2007). • Only a minority of females, approximately 5 to 8%, will experience recurrent vulvovaginal candidiasis (RVVC), defined as ≥ 3 episodes of <i>Candida</i> vulvovaginitis per year (Sobel 2007; Sobel 2016) • Host, genetic, and behavioral factors all play a role in whether a woman may be more susceptible to developing VVC. These risk factors facilitate the transformation from asymptomatic colonization to symptomatic vaginitis (Sobel 2016). • Of note, at least 20% of all females are colonized vaginally with <i>Candida</i> species. During pregnancy this increases to 30%.	• While most females will experience at least one VVC infection in their lifetime, a minority of females (an estimated 5 to 8%) will experience RVVC, defined as ≥ 3 episodes of <i>Candida</i> vulvovaginitis per year, in their lifetimes.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Uncomplicated VVC is often treated effectively with a short-course of an oral or a topical azole formulation (i.e., single dose and regimens of 1–3 days), which achieves relief of symptoms and negative cultures in 80% to 90% of patients who complete therapy (Workowski et al. 2021). • There are presently no FDA approved therapies for the treatment and/or prevention of RVVC. Most recommended therapies for this condition are prescribed off-label (Sobel et al. 2004; Workowski et al. 2021). • In their 2021 sexually transmitted infections (STI) guidelines, Centers for Disease Control and Prevention (CDC) recommends, for the treatment of RVVC, a longer duration initial regimen (e.g., 7-14 day topical therapy or fluconazole every 72 hours for a total of 3 doses) followed by a weekly maintenance regimen of oral fluconazole for 6 months to induce and then maintain mycologic remission (Workowski et al. 2021). • Treatment guidelines, including those from the American College of Obstetricians and Gynecologists (ACOG) and the Infectious Diseases Society of America (IDSA), recommend oral or topical agents, typically two agents divided into a short course induction regimen followed by a longer maintenance regimen, for the management of RVVC (The American College of Obstetricians and Gynecologists 2006; Pappas et al. 2016). • Studies have demonstrated that even a six-month period of effective suppressive prophylaxis for RVVC does not guarantee a cure during the subsequent six months after suppressive therapy has been discontinued (Sobel et al. 2004).	• There are presently no FDA approved therapies for RVVC. • CDC recommends combined induction and maintenance regimens to attempt to achieve mycologic remission. • Even after six months of suppressive prophylaxis, sustained remission of recurrent VVC episodes is difficult to achieve after suppressive therapy has been discontinued (Sobel 2016).

Benefit		
	• The efficacy of oteseconazole for reducing the incidence of RVVC was evaluated in two randomized, placebo-controlled trials, CL-011 and CL-012. Both trials consisted of two phases: an open-label induction phase and an 11-week maintenance phase. Patients received three sequential doses of 150 mg of fluconazole during the induction phase. Patients returned 14 days after the first dose of fluconazole and if the acute VVC episode was resolved (vulvovaginal signs and symptoms score <3), they were randomized (2:1) to receive either 150 mg of oteseconazole or placebo for 7 days followed by 11 weekly doses in the maintenance phase. Efficacy was assessed by the proportion of patients with ≥ 1 culture verified acute VVC episode (positive fungal culture for <i>Candida</i> species associated with a clinical signs and symptoms score of ≥ 3) during the maintenance phase through Week 48. • Oteseconazole was superior to placebo in the proportion of patients with ≥ 1 culture verified acute VVC episode through Week 48 and the proportion of patients with ≥ 1 KOH-verified acute VVC episode through Week 48. • A third trial, CL-017, evaluated the efficacy and safety of oteseconazole versus fluconazole and placebo in postmenarchal females with RVVC who presented with an acute VVC episode. The trial consisted of two phases: an induction and a maintenance phase. Patients received 1050 mg of oteseconazole over two days (600 mg [4x150 mg] on Day 1 and 450 mg [3x150 mg] on Day 2) or three sequential doses of 150 mg of fluconazole (every 72 hours). Patients returned 14 days after the first doses and entered the maintenance phase only if the acute VVC episode was resolved. During the maintenance phase, patients received 150 mg oteseconazole weekly or placebo weekly for 11 weeks. Efficacy was assessed by the proportion of subjects with ≥ 1 culture-verified acute VVC episode during the maintenance phase (post-	• Oteseconazole is effective for reducing the incidence of recurrent VVC in postmenarchal patients with a history of RVVC. Two regimens are effective: induction with fluconazole followed by maintenance with oteseconazole, and an oteseconazole-only regimen for both induction and maintenance. •  (b) (4) • The Applicant provided insufficient information to support indications for oteseconazole  (b) (4).  (b) (4) Additional placebo-controlled studies will be needed to support these indications.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	randomization through Week 50) or those subjects who failed to clear their infection during the induction phase. - Oteseconazole was superior to fluconazole/placebo in the proportion of patients with ≥ 1 culture verified recurrent acute VVC episode during the maintenance phase (post randomization through Week 50) or who failed clearing their infection during the induction phase. - The Applicant's proposed indications were (b) (4) (b) (4) (b) (4) However, the available evidence supports only an indication for the reduction of recurrence of VVC. - The Applicant proposed (b) (4) (b) (4) (b) (4)	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- Ocular abnormalities such as cataracts, opacities, and exophthalmos/buphthalmos were observed in the offspring of pregnant rats dosed at 7.5 mg/kg/day during pre- and postnatal developmental studies. - The safety profile of oteseconazole, as demonstrated in three phase 3 clinical trials, was found to be mostly benign. Urinary tract infections, bacterial vaginosis, headache, nausea, abdominal pain, pyrexia and diarrhea occurred in ≥2% of all oteseconazole exposed subjects in the phase 3 trials. - Transient, largely asymptomatic, unexplained elevations in creatine phosphokinase (CPK) of ≥10 x ULN, with no associated symptoms of myalgias, muscle weakness, evidence of myoglobinuria or creatinine elevations were observed in oteseconazole treated subjects while on treatment and up to 5 to 8 months post-therapy (all within 2 half-lives).	- Pre-clinical ocular findings found in rat pups along with oteseconazole’s prolonged drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) will result in contraindication of this drug for pregnant and lactating females as well as females of reproductive potential. - Headache, nausea and CPK elevations occurred more commonly in the oteseconazole arm than in the comparator/placebo arm and will be described in product labeling.

*(Sobel et al. 2004; Sobel 2007; Kourtis et al. 2014; Sobel 2016; Workowski et al. 2021; The American College of Obstetricians and Gynecologists 2006; Pappas et al. 2016)

2.2. Conclusions Regarding Benefit-Risk

Vulvovaginal candidiasis is a common condition. Approximately 70 to 75% of females experience an episode of VVC in their lifetime and 40 to 50% of these females will experience a recurrence. While VVC may result in significant discomfort and affect patients' everyday life, it is not a life-threatening condition and is not usually associated with serious health consequences. VVC is treated with 1 to 3 days of oral or topical azoles and 80% to 90% of patients achieve relief of symptoms. While there are treatments approved for acute VVC, no therapies are approved for reduction of RVVC episodes.

Oteseconazole is an azole antifungal drug that was proposed (b) (4). One of the distinguishing characteristics of oteseconazole is its prolonged drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole).

The application was supported by three adequate and well controlled phase 3 trials. The trials consisted of an induction phase to treat an acute episode of RVVC and a maintenance phase. In two trials the acute VVC episode was treated with fluconazole. In the third trial either fluconazole or oteseconazole was used for induction. In all three trials in the maintenance phase patients received either oteseconazole or placebo, and in all three trials oteseconazole was found to be superior to placebo in the proportion of patients with ≥ 1 acute VVC episode up to Week 50 post-randomization. The safety profile of oteseconazole in the three phase 3 clinical trials was comparable to the comparator regimens.

However, the evidence demonstrating the efficacy of oteseconazole (b) (4) was found to be insufficient (b) (4).

In addition, ocular abnormalities were observed in pre- and postnatal developmental studies. Given that a long drug exposure window of oteseconazole precludes reliable use of contraceptive measures, it was recommended to contraindicate oteseconazole for pregnant and lactating females as well as females of reproductive potential.

Consequently, the recommended indication for oteseconazole is to reduce the incidence of RVVC in females with a history of RVVC who are not of reproductive potential.

II. Interdisciplinary Assessment

3. Introduction

Oteseconazole (VT-1161, OTE) is an azole antifungal metalloenzyme inhibitor targeting the fungal sterol, 14 α demethylase (CYP51), which mediates fungal membrane permeability. The clinical development program for oteseconazole commenced in 2011 and resulted in the May 2021 submission of NDA 215888, which is the subject of this Integrated Review.

The Applicant is seeking approval for the following indications:



Key regulatory highlights in the oteseconazole development program include: the granting of both Fast Track and Qualified Infectious Disease Product designations for the treatment of VVC and RVVC in September 2016; an End of Phase 2 meeting in August 2017, where the phase 3 development program was discussed; and a type B pre-NDA meeting in November 2020, where key discussion topics for this review such as the pre- and postnatal development animal study findings and the proposed indications were discussed.

Literature estimates indicate that VVC affects between 70 to 75% of females at least once during their lives, with females between the ages of 25 and 34 being the most frequently affected. VVC is characterized by acute itching, vaginal discharge, or symptoms of vaginal irritation, such as burning and soreness. *Candida albicans* accounts for 85 to 95% of all *Candida spp.* isolated from the vagina. Forty to fifty percent of all females will experience a recurrence of VVC and 5 to 8% of all adult females will have RVVC. The CDC defines RVVC as having three or more episodes of VVC in a 12-month period, whereas the Infectious Diseases Society of America (IDSA) and ACOG define RVVC as having four or more episodes of VVC in a 12-month period. For the purposes of this NDA, the CDC definition of three or more episodes of VVC in a 12-month period was adopted (Sobel 2007; Workowski et al. 2021).

Presently, there are no FDA approved therapeutic options for the treatment of RVVC. Recommended regimens include short course oral (e.g., fluconazole) or topical induction regimens (3 to 7 days) for the acute VVC infection, followed by a 6-month maintenance regimen typically given at 1-week intervals. Studies have shown that upon cessation of therapy, "approximately 50% of women will develop a culture positive episode of RVVC within 3 to 4 months" (Sobel 2016; Workowski et al. 2021).

The efficacy and safety of oteseconazole were supported by three phase 3 clinical trials: CL-011, CL-012, and CL-017. Key issues identified during review of this application are listed below and discussed in Sections [6.3](#) and [7.7](#).

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Assessment of the Use of VVC Medication on the Interpretation of the Efficacy of Oteseconazole

3.1.1.2. [REDACTED] (b) (4)

3.1.1.3. Support for Proposed Indications

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Nonclinical Ocular Findings and Implications for Labeling

3.1.2.2. CPK Elevations

3.2. Approach to the Review

[Table 3](#) provides an overview of the major clinical trials conducted by the Applicant during the oteseconazole clinical development program. Trials CL-011 and CL-012 provided support for the approval of oteseconazole for the reduction of RVVC using a dosage regimen of induction with fluconazole followed by maintenance with oteseconazole. Trial CL-017 provided support for an alternative dosing regimen using oteseconazole for both induction and maintenance.

The primary sources of safety data were the treatment-emergent adverse events and laboratory data from Trials CL-011, CL-012, and CL-017. The phase 2b dose-finding trial, Trial CL-006, was not analyzed in support of efficacy but was reviewed to supplement safety information. Additional safety data were provided by phase 1 studies and studies for other indications. The 120-day safety update is discussed in Section [7.6.7.3](#).

The trials submitted by the Applicant were sufficient to establish the safety and efficacy of oteseconazole for reducing the incidence of RVVC in the indicated population. They were not sufficient to support the requested indications [REDACTED] (b) (4)

[REDACTED] (b) (4)

The key benefit and risk issues are addressed under Sections [6.3](#) and [7.7](#), respectively, of this NDA review.

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
CL-011	Female subjects ≥12 years of age with RVVC.	Phase 3 Control Type: PC; PG Randomization: 2:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug (established name): Oteseconazole Dose: Induction: FLU 150 mg on D1, 4 and 7 Maintenance: OTE 150 mg once daily for 7 days, followed by OTE 150 mg once weekly for 11 weeks Or matching placebo regimen Number treated: 217 OTE 109 Placebo Duration (quantity and units): 12 weeks	Primary: Proportion of subjects with ≥ 1 culture verified acute VVC episodes during the Maintenance Phase (post-randomization through Week 48) in the ITT population. Secondary: Time to first recurrence of a culture verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase. Proportion of subjects with at least 1 positive culture for <i>Candida</i> species during the Maintenance Phase Proportion of subjects with at least 1 culture-verified acute VVC episode with signs and symptoms score of ≥3 post-randomization through Week 24	Planned: 300 Actual: 326	Centers: 97 Countries: 6

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
CL-012	Female subjects ≥12 years of age with RVVC.	Phase 3 Control Type: PC; PG Randomization: 2:1 Blinding: DB Biomarkers: None Innovative design features: None	Drug (established name): Oteseconazole Dose: Induction: FLU 150 mg on D1, 4 and 7 Maintenance: OTE 150 mg once daily for 7 days, followed by OTE 150 mg once weekly for 11 weeks Or matching placebo regimen Number treated: 217 OTE 110 Placebo Duration (quantity and units): 12-weeks	Primary: Same as CL-011 Secondary: Same as CL-011	Planned: 300 Actual: 330	Centers: 84 Countries: 6

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
CL-017	Female subjects ≥12 years of age with RVVC.	Phase 3 Control Type: Active/Placebo-controlled (FLU and PLB); PG Randomization: 2:1 Blinding: DB, DD (induction only) Biomarkers: None Innovative design features: None	Drug (established name): Oteseconazole Dose: Induction: OTE 600 mg on D1 and 450 mg on D2 Maintenance: OTE 150 mg once a week for 11 weeks Or Induction: FLU 150 mg on D1, 4 and 7 Maintenance: Placebo once a week for 1 weeks Number treated: 146 OTE 72 FLU/Placebo Duration (quantity and units): 12-weeks	Primary: The proportion of subjects who failed initial treatment or with ≥1 culture verified acute VVC episode, post-randomization, through Week 50 in the ITT population. Secondary: Proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with oteseconazole or fluconazole. Proportion of subjects with at least 1 culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase (post-Day 14 through Week 50). Time to first recurrence of a culture-verified acute VVC episode with	Planned: 180 Actual: 219	Centers: 51 Countries: 1

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
CL-006	Adult females 18-64 years with RVVC.	Phase 3 Control Type: PC; PG; Dose-ranging Randomization: Standard Blinding: DB Biomarkers: None Innovative design features: None	Drug (established name): Oteseconazole Dose: OTE 150 mg daily on Days 1-7 then once weekly on Weeks 2-12, followed by placebo once weekly on Weeks 13- 24 OTE 150 mg daily on Days 1-7 then once weekly on Weeks 2-24 OTE 300 mg daily on Days 1-7 then once weekly on Weeks 2-12, followed by placebo once weekly on Weeks 13- 24 OTE 300 mg daily on Days 1-7 then once weekly on Weeks 2-24	signs and symptoms score ≥ 3 during the Maintenance Phase (post-Day 14 through Week 50). Proportion of subjects with at least 1 positive culture for <i>Candida</i> species during the Maintenance Phase. Primary: Proportion of subjects with ≥ 1 culture verified acute VVC episodes during the Maintenance Phase through Week 48 in the ITT population. Secondary: Proportion of subjects with culture verified acute VVC infection through Week 24. Proportion of subjects with culture-verified acute VVC infection from Week 24 through week 48 of the study Time to first recurrence of culture-	Planned: 200 Actual: 254	Centers: 38 Countries: 1

Trial Identifier	Trial Population	Trial Design	Regimen, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
			Placebo daily on Day 1-7 then once weekly on Weeks 2-24 Number treated: 41 150 mg (12 weeks) 42 150 mg (24 weeks) 42 300 mg (12 weeks) 41 300 mg (24 weeks) 45 placebo Duration (quantity and units): 12 or 24-weeks	verified acute VVC infection		

Source: Clinical Study Report and adsl.xpt

Abbreviations: DB, double-blind; DD: double-dummy; FLU, Fluconazole; ITT, intent to treat; OL, open-label; OTE, Oteseconazole; PC, placebo-controlled; PG, parallel group; PK, pharmacokinetics; RVVC, recurrent vulvovaginal candidiasis; VVC, vulvovaginal candidiasis

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Section 6. Assessment of Effectiveness
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology properties of oteseconazole were comprehensively evaluated and are summarized in [Table 5](#).

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information Pharmacologic Activity	
	Established pharmacologic class (EPC)	Oteseconazole is an azole antifungal
Mechanism of action	Oteseconazole inhibits fungal lanosterol demethylase (CYP51) which catalyzes an early step in the conversion of lanosterol to ergosterol, which is required for fungal cell wall formation. Interruption of this conversion results in depletion of ergosterol, inhibition of fungal cell growth and increased fungal cell wall permeability.	
Active moieties	The active moiety is oteseconazole	
QT prolongation	At the dose evaluated in the thorough QT study (600 mg on Days 1-13 and 1200 mg on Day 14), which yielded peak exposures ~5 times the C _{max} associated with the recommended dosing regimen in the maintenance phase, oteseconazole did not prolong the QT interval to a clinically significant extent. A mean reduction of the QTcF (upper 90% confidence interval) of -5.6 milliseconds (-10.5 milliseconds) was observed and this effect was oteseconazole concentration-dependent.	
	General Information	
Bioanalysis	Validated LC/MS/MS methods were used to quantify oteseconazole concentrations in human plasma, blood, urine, and feces as relevant to individual studies.	
Healthy subjects versus patients	The PK of oteseconazole is similar in healthy subjects and subjects with VVC.	
Drug exposure following the therapeutic dosing regimen	PK Parameter	Mean (±SD) ^a
	C _{max} (µg/mL)	2.78 (1.25)
	AUC _{24h} (h·µg/mL)	64.2 (29.4)
	C _{min} (µg/mL)	2.53 (1.19)
	^a Based on population PK simulated exposures at Week 13 (end of treatment) in Phase 1 and 2 subjects weighing ~70 kg administered oteseconazole 600 mg on Day 1 followed by 450 mg on Day 2 then 150 mg weekly beginning on Day 14 for 11 weeks.	
Range of effective dosage(s) or exposure	The relationships between oteseconazole Day 14 exposure and the endpoint of recurrence of culture-verified acute episodes of VVC in the maintenance phase in Phase 3 trials was flat across the range of oteseconazole Day 14 exposures observed following a regimen of 150 mg QD for 7 days in studies CL-011 and CL-012, and a regimen of 600 mg QD on Day 1 and 450 mg on Day 2 in Study CL-017.	
Maximally tolerated dosage or exposure	An MTD was not determined. The highest single and multiple doses evaluated in humans, both of which were evaluated in the TQT trial were 1200 mg and 600 mg daily for 14 days, respectively. The highest dose evaluated in the MAD study was 320 mg QD for 7 days.	

Characteristic	Drug Information			
Dosage proportionality	Oteseconazole exposures increased in a dose-proportional manner while C _{max} increased less than dose-proportionally over a dose range of 20 to 320 mg.			
Accumulation	Mean accumulation ratio following daily dose administration for 7 days was 4.5 to 6.2 for a dose range of 40 to 320 mg.			
Bridge between to-be-marketed and clinical trial formulations	The to-be-marketed formulation was identical to the Phase 3 trial formulation except in appearance of the capsule shell.			
Absorption				
Bioavailability	Absolute bioavailability of oteseconazole was not determined. Based on the recovery of radiolabeled oteseconazole in the human mass balance study, it is estimated to be ~75%.			
T _{max}	4.0 - 9.67 h			
Food effect (fed/fasted) Geometric least square mean and 90% CI	Meal Type	AUC GMR (90% CI)	C_{max} GMR (90% CI)	T_{max} (h)
	High-fat, high-calorie meal versus fasted	1.36 (1.15 – 1.60)	1.45 (1.19 – 1.77)	Prolonged from 5 h (fasted) to 6.7 (fed, high-fat meal)
	Low-fat, low-calorie meal versus fasted	1.02 (0.86 – 1.21)	1.17 (0.95 – 1.43)	4.9
A high-fat, high-calorie meal was defined as 900-1000 kcal with 500-600 kcal from fat. A low-fat, low-calorie meal was defined as 650 kcal with 117 kcal from fat.				
Distribution				
Volume of distribution	423 L			
Plasma protein binding	≥ 99.5% at oteseconazole concentrations of 0.26 – 2.5 µg/mL.			
Drug as substrate of transporters	Oteseconazole is not a substrate of P-gp, BCRP, OATP1B1/B3, OAT1/3 or OCT2 transporters. It is unknown whether oteseconazole is a substrate of the MATE transporter.			
Elimination				
Mass balance results	Following administration of 600 mg [¹⁴ C]oteseconazole, 82% of the administered dose was recovered in excreta; 56% was recovered in feces and 26% was recovered in urine. No metabolites were identified.			
Clearance	0.253 L/h			
Half-life	Median terminal half-life is 138 days (for subject weighing 70 kg)			
Metabolic pathway(s)	No oteseconazole metabolites were detected in incubations with pooled human liver microsomes or in human mass balance studies.			
Primary excretion pathways (% dosage)	Oteseconazole appears to be primarily excreted by biliary excretion. An estimated 66% of the absorbed dose is excreted in feces, and 34% is excreted in urine.			

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	The predicted oteseconazole AUC in subjects weighing <40 kg was up to 2-fold higher than the AUC in subjects with body weight 60 – 70 kg. Because only 1 subject weighing <40 kg (actual weight 36 kg) was identified across Phase 3 clinical studies, the clinical significance of this observation is unknown.
Age	No clinically significant differences in the PK of oteseconazole were observed based on age.
Renal impairment	PopPK analyses indicate that mild to moderate renal impairment (eGFR 30-89 mL/min based on the MDRD equation) does not significantly alter the elimination of oteseconazole. However, use of oteseconazole is not recommended in the setting of severe renal impairment or ESRD due to the potential for increased drug accumulation.
Hepatic impairment	The effect of hepatic impairment on the PK of oteseconazole was not evaluated. Because biliary excretion appears to be the primary elimination pathway for oteseconazole, increased accumulation of oteseconazole may occur in the setting of hepatic impairment. Mild impairment (Child-Pugh A) is not expected to significantly alter the elimination of oteseconazole. However, use of oteseconazole is not recommended in the setting of moderate to severe hepatic impairment (Child-Pugh B-C) due to the potential for increased drug accumulation.
Drug Interaction Liability (drug as perpetrator)	
Inhibition/induction of metabolism	In vitro, oteseconazole was an inducer and inhibitor of CYP3A4/5. In vivo, coadministration of oteseconazole with midazolam (CYP3A4 substrate) did not result in clinically significant inhibition or induction of midazolam metabolism.
Inhibition/induction of transporter systems	In vitro, oteseconazole was an inhibitor of BCRP. Results of clinical drug-drug interaction studies indicate that oteseconazole had no clinically meaningful effect on the PK of digoxin (P-gp substrate). Results of clinical drug-drug interaction studies indicate that coadministration of oteseconazole with rosuvastatin (BCRP substrate) resulted in a clinically significant increase in rosuvastatin exposure.

Abbreviations: AUC, area under the curve; AUC₂₄, area under the curve at 24 hours; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CYP, cytochrome P450 isoenzyme; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; GMR, geometric mean ratio; LC/MS/MS, liquid chromatography with tandem mass spectrometry; MATE, multidrug and toxic compound extrusion; MDRD, modification of diet in renal disease; OATP, organic anion transporting polypeptides; P-gp, P-glycoprotein; PK, pharmacokinetics, TQT, thorough QT.

5.1. Nonclinical Assessment of Potential Effectiveness

Clinical Microbiology

In Vivo Activity

The activity of oteseconazole was evaluated in two studies using an estrogen-dependent murine model of vaginal candidiasis. In the first study, mice were rendered pseudo-estrus with the administration of estradiol and subsequently infected with a wild-type strain of *C. albicans*. At daily doses of 4, 10, or 25 mg/kg administered by oral lavage for 4 days, oteseconazole treatment yielded >90% reduction in vaginal lavage fluid fungal burden compared to vehicle (1 day following completion of treatment). Additionally, the 25 mg/kg dose of oteseconazole maintained antifungal activity similar to that of fluconazole through 4 days post-completion of treatment. For each dose level, oteseconazole plasma and vaginal tissue levels assessed 4 days after completion of treatment were comparable. Based on these studies, a threshold oteseconazole plasma concentration of ≥ 1 $\mu\text{g/mL}$ (which was associated with the 4 mg/kg dose) was used to inform dose selection in clinical efficacy trials.

In a second study conducted in the same murine model of vaginal candidiasis, the activity of oteseconazole and fluconazole were evaluated against 3 clinical isolates resistant to fluconazole (with oteseconazole minimum inhibitory concentrations [MICs] of ≤ 0.015 , 0.12 and 2 $\mu\text{g/mL}$). Overall, at the same dose level (25 mg/kg daily for 4 days), oteseconazole achieved a greater reduction in fungal burden compared to fluconazole.

In Vitro Activity

Oteseconazole demonstrated activity with minimum inhibitory concentration to inhibit growth of 90% of organisms (MIC_{90}) values ranging from <0.005 to 4 mcg/mL against *Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, and *C. auris*. The oteseconazole MIC range and MIC_{90} against approximately 1433 isolates of *C. albicans* were <0.0005 - >0.25 mcg/mL and 0.008-0.03 mcg/mL, respectively. Against 68 fluconazole resistant isolates, the MIC range and MIC_{90} were ≤ 0.015 to >8 mcg/mL and 1 mcg/mL, respectively. Against approximately 332 isolates of *C. glabrata*, the oteseconazole response MIC range and MIC_{90} were ≤ 0.015 to 1 mcg/mL and 0.125-1 mcg/mL, respectively. Against 58 isolates of *C. parapsilosis*, the MIC range and MIC_{90} values were ≤ 0.0005 to 0.12 mcg/mL and 0.05 to 0.15 mcg/mL, respectively. Against 50 isolates of *C. krusei* the MIC range and MIC_{90} were ≤ 0.015 to 1 mcg/mL and 0.5 mcg/mL, respectively. Against 21 isolates of *C. tropicalis*, the MIC range and MIC_{90} values were 0.004 to 0.015 mcg/mL and 0.06 to 0.15 mcg/mL, respectively. Against 15 isolates of *C. lusitaniae*, the MIC range and MIC_{90} values were 0.01 to 0.25 mcg/mL and 0.2 mcg/mL, respectively, and against 100 isolates of *C. auris*, the MIC range and MIC_{90} values were ≤ 0.015 to >8 mcg/mL and 4 mcg/mL, respectively.

For the three phase 3 studies, vaginal specimens (swabs) were collected at screening and at all scheduled and unscheduled visits where recurrent vulvovaginal candidiasis was suspected. A potassium hydroxide (KOH) preparation or Gram stain was performed on all specimens at baseline/screening and at selected visits. Specimens for fungal culture were collected and sent to the Central Laboratory (b) (4) for fungal isolation, identification, and

susceptibility testing. Specimens were collected to rule out bacterial vaginosis, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis*.

In vitro susceptibilities were determined by broth micro dilution methods according to the Clinical and Laboratory standards Institute Standard, Method M27:3 -*Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved. Standard-4th Edition*.

Studies CL-011, CL-012, and CL-017 were randomized, double-blind, placebo controlled, parallel group studies with an open-label induction phase, and all subjects had a history of RVVC. The subjects from CL-011 and CL-012 were selected from Europe and the United States, while the subjects in CL-017 were selected primarily within the United States. [Table 6](#) depicts the MIC values (range, inhibit growth of 50% [MIC₅₀] and MIC₉₀) of the two most common *Candida* species identified in the three phase 3 studies. In CL-011, the MIC range, MIC₅₀ and MIC₉₀ for *C. albicans* were ≤0.0005 to 0.12 mcg/mL, 0.002 mcg/mL and 0.008 mcg/mL, respectively. The MIC range, MIC₅₀, and MIC₉₀ for *C. glabrata* were 0.002 to 0.125 mcg/mL, 0.015 mcg/mL, and 0.06 mcg/mL, respectively. In CL-012 the range, MIC₅₀, and MIC₉₀ were ≤0.0005 to >0.25 mcg/mL, 0.002 mcg/mL, and 0.03 mcg/mL for *C. albicans*. For *C. glabrata* the range, MIC₅₀, and MIC₉₀ were 0.001 to >0.25 mcg/mL, 0.03 mcg/mL, and 0.125 mcg/mL, respectively. The OTE MIC range, MIC₅₀, and MIC₉₀ for *C. albicans* for all isolates in CL-017 were ≤0.0005 to >0.25 mcg/mL, 0.004 mcg/mL, and 0.06 mcg/mL and the FLU range, MIC₅₀, and MIC₉₀ were ≤0.06 to 16 mcg/mL, 0.25 mcg/mL, and 8 mcg/mL.

Table 6. A Comparison of MIC Values From Isolates for Three Phase 3 Studies

<i>Candida</i> spp.	CL-011		CL-012		CL-017	
	MIC mcg/mL	MIC mcg/mL	MIC mcg/mL	MIC mcg/mL	MIC mcg/mL	MIC mcg/mL
	OTE	FLU	OTE	FLU	OTE	FLU
<i>C. albicans</i>	≤0.0005	<0.06	≤0.0005	≤0.06	≤0.0005	<0.06
Range	- 0.12	-16	->0.25	->32	->0.25	-16
MIC ₅₀	0.002	0.12	0.002	0.25	0.004	0.25
MIC ₉₀	0.008	2	0.03	4	0.06	8
<i>C. glabrata</i>	0.002	0.06	0.001	≤ 0.06	0.002	0.125
Range	-0.12	8	->0.25	-32	>0.25	-16
MIC ₅₀	0.15	1	0.03	1	0.03	2
MIC ₉₀	0.06	2	0.125	16	0.125	8

Source:
Abbreviations: MIC, minimum inhibitory concentration.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant’s proposed dosing regimen (b) (4) is as follows:

- Day 1: administer oteseconazole 600 mg (as a single dose) orally
- Day 2: administer oteseconazole 450 mg (as a single dose) orally, then
- Beginning on Day 14: administer oteseconazole 150 mg orally once a week (every 7 days) for 11 weeks (Weeks 2 through 12)

The 2-day starting dose of oteseconazole was only evaluated in one phase 3 trial (CL-017). In the other phase 3 trials (CL-011 and CL-012), treatment was initiated with three doses of 150 mg

fluconazole administered 72 hours apart, followed by a 12-week maintenance phase of oteseconazole as follows:

- Day 1, Day 4, and Day 7: administer fluconazole 150 mg orally
- On Days 14 through 20: administer oteseconazole 150 mg orally once daily for 7 days
- Beginning on Day 28: administer oteseconazole 150 mg orally once a week (every 7 days) for 11 weeks (Weeks 4 through 14)

The 7-day 150 mg daily dosing regimen used in trials CL-011 and CL-012 mirrors the low-dose regimen shown to be efficacious in the phase 2b trial, CL-006. Additionally, this regimen was expected to yield oteseconazole plasma concentrations ≥ 1 $\mu\text{g/mL}$, which were associated with a significant reduction in fungal burden in the murine model of vaginal candidiasis. Although the 2-day starting dose regimen used in the CL-017 trial was not evaluated in the phase 2 trials, it was predicted (and shown) to achieve Day 14 minimum plasma concentration (C_{min}) values comparable to the 7-day 150 mg daily dosing regimen as summarized in [Table 7](#). Additionally, simulated exposures for the 2-day and the 7-day regimens reflect comparable area under the concentration-time curve during the dosing interval (AUC_{τ}) at Day 14 (i.e., 234.3 $\mu\text{g}\cdot\text{h/mL}$ versus 236.7 $\mu\text{g}\cdot\text{h/mL}$, respectively) as shown in [Figure 1](#).

The 150 mg weekly dosing regimen selected for the three phase 3 trials was informed by the pharmacokinetics (PK), efficacy, and safety of oteseconazole in a phase 2b dose-ranging study which evaluated the dosing regimen of 150 mg daily for 7 days, followed by 150 mg weekly for 11 weeks beginning on Day 14 (in addition to 3 other oteseconazole dosing regimens and placebo) for the prevention of recurrence of VVC after induction with fluconazole. The primary endpoint, which was the proportion of subjects with ≥ 1 culture-verified acute VVC episode during the maintenance phase through Week 48 of the study, was statistically significantly lower for the 12-week 150 mg dosing regimen compared to placebo (4.8% versus 24%, p-value < 0.0001). Furthermore, the 12-week 150 mg dosing regimen, which was the lowest dose and shortest duration of oteseconazole administration in this study, exhibited comparable efficacy to the higher dose and longer duration dosing regimens.

In the CL-011 and CL-012 trials, fluconazole/oteseconazole was superior to fluconazole/placebo with respect to the proportion of subjects with ≥ 1 culture-verified acute VVC episode through Week 48. Similarly, in Trial CL-017, treatment with the oteseconazole-only regimen was superior to fluconazole/placebo in the proportion of subjects with ≥ 1 culture-verified acute VVC episode through Week 50 (see Section [6.2](#) for detailed discussion of phase 3 efficacy results).

Based on these results, the review team has proposed the following dosing regimens for the revised indication of reduction of RVVC:

- An oteseconazole-only regimen comprised of:
 - 600 mg on Day 1
 - 450 mg on Day 2
 - 150 mg weekly for 11 weeks beginning on Day 14 post-initiation of treatment

- Or, fluconazole followed by oteseconazole:
 - 150 mg fluconazole on Days 1, 4 and 7
 - 150 mg oteseconazole once daily for 7 days beginning on Day 14
 - Oteseconazole 150 mg weekly for 11 weeks beginning on Day 28 post-initiation of treatment

Table 7. Oteseconazole Minimum Plasma Concentrations Observed in Phase 2b and Phase 3 Trials

Study	Oteseconazole Dosing Regimen	Day 14 Plasma Concentration (µg/mL) Mean (SD)	Maintenance Phase Week 12 ^a Plasma Concentration (µg/mL) Mean (SD)
CL-017	600 mg on Day 1 and 450 mg on Day 2, followed by 150 mg QW for 11 weeks	1.4 (0.7)	2.7 (1.3)
CL-012	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.8 (0.7)	3.6 (1.5)
CL-011	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.7 (0.9)	3.4 (2.0)
CL-006	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.4 (0.7) ^b	2.6 (1.4)

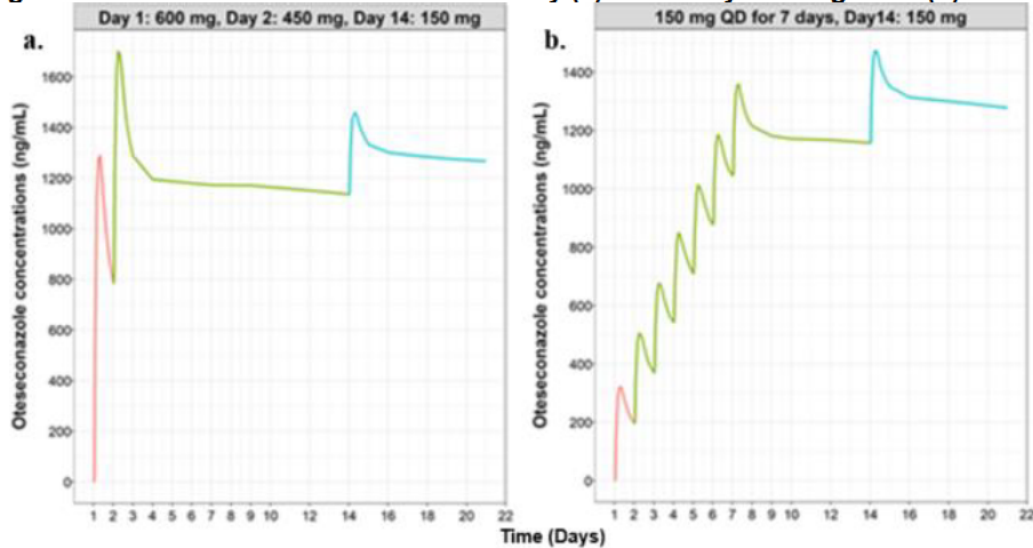
Abbreviations: QD=once daily; QW=once weekly; SD=standard deviation

a. Week 14 in CL-017 and Week 12 in CL-012/CL-011 are both post 11 weeks of 150 mg QW dosing, i.e., at the end of Maintenance Phase in all 3 studies.

b. Day 7 plasma concentration; Day 14 was not assessed in CL-006.

Source: CL-017 CSR Table 11-31, CL-012 CSR Table 11-28, CL-011 CSR Table 11-28, and CL-006 CSR Table 11-27

Figure 1. Oteseconazole PK Profiles for 2-Day (a) and 7-Day Starting Dose (b)



Source: Reviewer analysis
Abbreviations: PK, pharmacokinetic; QD, daily.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial CL-011

6.2.1.1. Design, Trial CL-011

Trial CL-011 was a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of oteseconazole oral capsules for the prevention of VVC episodes in females with a history of RVVC. The design of the study followed advice provided by the Division during reviews of the protocol and supports the indication for reducing the incidence of recurrence of VVC. The full protocol synopsis is contained in Section [15](#) of this review.

Subjects presenting with an acute VVC infection and a history of RVVC entered the induction phase and were treated with fluconazole. All subjects received three sequential 150 mg oral doses (every 72 hours) of fluconazole. Approximately 14 days after receipt of fluconazole, consented females were evaluated for resolution of their acute VVC episode. Females documented as having a signs and symptoms score of <3 were eligible for the 12-week maintenance phase and were subsequently randomized in a 2:1 ratio to receive either oteseconazole or matching placebo for 7 daily doses (1 week) of 150 mg, followed by 11 weekly doses of 150 mg, and then a 36-week follow-up period. The baseline/Day 1 visit was defined as the first day the study drug was received. Females whose acute VVC episodes were not resolved following fluconazole administration were considered screen failures.

Study visits during treatment were scheduled as follows: a screening visit, Day -14 (± 2 days); a baseline/end-of-induction visit, on Day 1; a Day 14 (± 2 days) visit, a Week 6 visit (± 7 days); and an end-of-treatment visit Week 12 (± 14 days). After the week 12 visit, subjects were followed every 6 weeks until the end of study visit at Week 48 (± 14 days).

Since the effect of oteseconazole for the treatment of an acute VVC episode was unknown, treatment of the acute VVC episode with fluconazole, a known effective treatment for VVC, was provided to all patients. Randomizing successfully treated patients following the induction phase allowed for a more controlled assessment of recurrence for oteseconazole versus placebo during the maintenance phase.

6.2.1.2. Eligibility Criteria, Trial CL-011

Eligible subjects were generally healthy nonpregnant, nonlactating postmenarchal females ≥ 12 years of age with a history of RVVC and an acute VVC infection at screening. A history of RVVC was defined as having had at least three episodes of acute VVC in the past 12 months, as evidenced by the following:

- Having an acute VVC episode at the time of screening, with a documented positive KOH or Gram stain performed at the investigational site
- Having had two or more *additional* episodes of acute VVC in the prior 12 months, with *at least one* of the episodes documented by a positive confirmatory laboratory test, i.e., culture, polymerase chain reaction, Affirm test, KOH test, Gram stain, a documented Papanicolaou (Pap) test.

The acute VVC infection at screening required a clinical diagnosis of symptomatic acute VVC (i.e., a total signs and symptom score ≥ 3) as well as a positive KOH wet mount preparation (or Gram stain) from a vaginal smear that demonstrated filamentous hyphae/pseudohyphae and/or budding yeast cells.

Eligible subjects were required to have a composite vulvovaginal signs and symptoms score of ≥ 3 at screening and a composite score of < 3 at the baseline visit, demonstrating acceptable resolution of the presenting VVC episode. Vulvovaginal signs (edema, erythema, and excoriation) and symptoms (burning, itching, and irritation) were assessed by the investigator and subject, respectively. The six signs and symptoms were scored based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) and the individual scores were summed to calculate the total composite vulvovaginal signs and symptoms score.

Subjects were ineligible for study participation if, at screening or on Day 1, they were noted to have the following key exclusionary criteria:

- Concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*)
- An active human papillomavirus infection, as evidenced by visible condylomas on vulvovaginal examination at screening and Day 1
- The presence or a history of another vaginal or vulvar condition(s) that in the investigator's opinion would have confounded the interpretation of clinical response
- Use of any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to screening or use of topical vulvar or vaginal steroids during the study or within 7 days prior to screening
- A laboratory abnormality that in the opinion of the investigator was likely to introduce additional risk to the subject or might interfere with data interpretation

Females were also excluded from study participation if they:

- Were found to be pregnant at screening
- Had active substance abuse
- Had uncontrolled diabetes mellitus
- Had either a history of or an active cervical/vaginal cancer

6.2.1.3. Statistical Analysis Plan, Trial CL-011

The primary efficacy endpoint was the occurrence of one or more culture-verified acute VVC episodes during the maintenance phase (post randomization through Week 48) in the intent-to-treat (ITT) population which included all randomized subjects. A culture-verified acute VVC episode during the maintenance phase (considered a recurrent episode) was defined as a positive culture for *Candida* species associated with a clinical signs and symptoms score of ≥ 3 .

Subjects who may have been treated with VVC medication during the maintenance phase were not automatically considered as having a recurrent episode. This is a concern as treatment with a VVC medication might indicate a VVC episode. This will be addressed in Section [6.3.1](#).

Key secondary endpoints included the following:

- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms of ≥ 3 during the maintenance phase.

- Proportion of subjects with at least one positive culture for *Candida* species during the maintenance phase. Note that this is the microbiologic portion of the primary endpoint only.
- Proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms of ≥ 3 post randomization through Week 24; note that this is the primary endpoint assessed at an earlier time point.
- Changes from screening through Week 48 in the 36-item short form survey (SF-36) mental component score (MCS) and patient reported outcome survey total score.

The primary method of analysis was a chi-square test for active treatment versus placebo based on the ITT population. Time to recurrence of a culture-verified acute VVC episode was estimated using the method of Kaplan-Meier. A chi-square test was used to compare the active treatment group to the placebo group for each key secondary endpoint that was a proportion. The changes from baseline value for the SF-36 MCS and SF-36 total score were analyzed using repeated measure analysis of covariance models with fixed effects for treatment group, time point, treatment by time point interaction and baseline value and with a random effect of subject. A compound symmetry covariance structure was used.

The hierarchical/gate-keeping method was used to control for the type I error rate of 0.05 for multiplicity of the key secondary endpoints (order as stated above).

For handling subjects with missing data, the primary analysis approach was to impute missing values using a multiple imputation approach. This was used for both intermittent missing data, i.e., when a subject had a missed visit or a missed assessment of signs and symptoms or missing culture results, or if a subject had terminal missing data, i.e., if a subject discontinued from the trial. The missing values were imputed using baseline information of region, treatment, baseline body mass index (BMI), baseline age, ethnicity and visit. Additional details of the multiple imputation methods are given in Section [15](#).

Additionally, sensitivity analyses were conducted using different methods for handling missing data. One method treats subjects with missing data as having had a recurrence. The analysis of time to recurrence censors subjects who discontinue the study.

Assuming a treatment difference in subjects with one or more culture-verified acute VVC episodes during the maintenance phase (post randomization through Week 48) of 35% between oteseconazole and placebo and assuming that 50% of subjects on placebo have a recurrence, a sample size of 68 active subjects and 34 placebo subjects was determined to provide at least 95% power to detect this difference. A total of 102 subjects was determined to provide more than 90% power to detect reasonable differences between treatment groups in most of the pre-specified key secondary endpoints. However, a sample size of 160 active subjects and 80 placebo subjects was needed to provide 80% power to detect a treatment difference of 3.9 between the oteseconazole treatment group and the placebo group in the change from screening through Week 48 in the SF-36 MCS with a standard deviation of 10 points. Approximately 300 subjects were anticipated to be necessary for randomization to arrive at approximately 240 evaluable subjects. Approximately 600 subjects would be screened to randomize approximately 300 subjects that would meet the inclusion/exclusion criteria.

6.2.1.4. Results of Analyses, Trial CL-011

Subject Disposition, Demographics and Baseline Characteristics

The trial was conducted at 97 sites in North America, Japan, and Europe. The first patient was enrolled on August 20, 2018, and the study was completed was on October 21, 2020.

All screened and randomized subjects are summarized below in [Table 8](#). A total of 553 subjects were screened. Among these 553 subjects, 438 subjects entered the induction phase. Following the induction phase, 326 subjects were randomized, in a 2:1 ratio and then entered into the maintenance phase. Two hundred seventeen subjects were randomized to oteseconazole and 109 to placebo. All randomized subjects were treated and received the study medication to which they were randomized. Therefore, the safety population and the ITT population are the same.

Table 8. Subjects Screened and Randomized, Trial CL-011

Disposition	N
No. patients screened	553
Entered Induction Phase	438
No. patients not randomized	112
No. patients randomized	326

Source: Reviewer conducted analysis using ADSL dataset

Subject disposition is summarized in [Table 9](#). Of the 326 subjects in the ITT population, 35 (16.1%) of 217 oteseconazole subjects and 18 (16.5%) of 109 placebo subjects were discontinued from the study. The most common reasons for discontinuation were withdrawal by subject (8.3%) and lost to follow-up (3.7%). The mean number of days (SD) of maintenance treatment in the ITT population was 79 (18.4) in oteseconazole and 80 (17.0) in placebo. Treatment compliance was high in both treatment arms. Daily compliance (defined as the number of doses taken divided by 7) during the daily dosing phase had a mean (SD) of 100% (4.7) for oteseconazole and 99% (6.8) for placebo. Compliance for the weekly dosing phase (number of doses divided by 11) was 93% (21.9) and 94% (19.8) in oteseconazole and placebo, respectively. The amount of follow-up was comparable for the two treatment arms with a mean (SD) follow-up time for oteseconazole subjects of 308.6 days (81.6) and 315.0 (77.0) days for placebo.

Table 9. Subject Disposition, Trial CL-011: ITT Population

Disposition Category	Oteseconazole N=217 n (%)	Placebo N=109 n (%)	Total N=326 n (%)
Patients randomized (ITT)	217 (100)	109 (100)	326 (100)
Patients treated (safety)	217 (100)	109 (100)	326 (100)
Completed treatment	149 (68.7)	82 (75.2)	231 (70.8)
Completed study	182 (83.9)	91 (83.5)	273 (83.7)
Discontinued study	35 (16.1)	18 (16.5)	53 (16.3)
Adverse event	1 (<1)	0 (0)	1 (<1)
Pregnancy	2 (<1)	1 (<1)	3 (<1)
Lost to follow-up	8 (3.7)	4 (3.7)	12 (3.7)
Withdrawal by subject	18 (8.3)	9 (8.3)	27 (8.3)
Sponsor request	2 (<1)	0 (0)	2 (<1)
Other	2 (<1)	2 (1.8)	4 (1.2)
Noncompliance	1 (<1)	0 (0)	1 (<1)
Investigator discretion	1 (<1)	1 (<1)	2 (<1)
Lab revealed clinically significant changes	0 (0)	1 (<1)	1 (<1)

Source: Reviewer conducted analysis using ADSL dataset

Abbreviation: ITT, intent to treat; N, number of subjects; n, number of subjects with at least one event.

Subjects' demographic and baseline characteristics, which were similar between the arms, are summarized for the ITT population in [Table 10](#). The mean age (SD) was 34 (10.2) years old. The majority of participants were between 25 to 34 years of age, 53.9% in the oteseconazole arm and 53.2% in the placebo arm. A single subject, randomized to the oteseconazole arm, was <18 years old, and only two participants, both in the oteseconazole arm, were ≥65 years old. A majority of subjects were White (72%) and Not Hispanic or Latino (92%). Latino females, most of whom identified as White, comprised 7.7% of the total ITT population.

Nearly equal percentages of subjects, 42.9% and 43.6%, across both treatment arms were from North America and Europe, respectively. The majority of North American subjects were from the United States, while most European subjects were from Eastern Europe. 13.5% of all subjects were from Japan.

Table 10. Demographics and Baseline Characteristics, Trial CL-011: ITT Population

Characteristic	Oteseconazole N=217 n (%)	Placebo N=109 n (%)	Total N=326 n (%)
Age group, years, n (%)			
Mean (SD)	34 (10.3)	34 (9.9)	34 (10.2)
Median (Min, Max)	33 (17, 78)	34 (14, 60)	33 (17, 78)
12 to 17	1 (<1)	0	1 (<1)
18 to 33	109 (50.2)	54 (49.5)	163 (50.0)
≥34	107 (49.3)	55 (50.5)	162 (49.7)
Sex			
Female	217 (100)	109 (100)	326 (100)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Asian	33 (15)	12 (11)	45 (14)
Black or African American	26 (12)	17 (16)	43 (13)
Other	1 (<1)	0	1 (<1)
White	156 (72)	80 (73)	236 (72)

Characteristic	Oteseconazole N=217 n (%)	Placebo N=109 n (%)	Total N=326 n (%)
Ethnicity, n (%)			
Hispanic or Latino	19 (9)	6 (6)	25 (8)
Not Hispanic or Latino	198 (91)	103 (94)	301 (92)
Country of participation, n (%)			
Bulgaria	50 (23)	23 (21)	73 (22)
Canada	8 (4)	8 (7)	16 (5)
Japan	32 (15)	12 (11)	44 (13)
Poland	33 (15)	24 (22)	57 (17)
United Kingdom	9 (4)	3 (3)	12 (4)
United States	85 (39)	39 (36)	124 (38)
Region			
North America	93 (43)	47 (43)	140 (43)
Europe	92 (42)	50 (46)	142 (44)
Japan	32 (15)	12 (11)	44 (13)
BMI (kg/m ²)			
Mean (SD)	24.9 (7)	25.8 (8)	25.2 (7)
Diabetes mellitus	5 (2)	5 (5)	10 (3)
Acute VVC episodes in past 12 months			
Mean (SD)	4 (2)	4 (2)	4 (2)
<4	120 (55)	54 (50)	174 (53)
≥4	97 (45)	55 (50)	152 (47)

Source: Adapted Table 14.1.2.1 and reviewer conducted analyses using ADSL
Abbreviations: BMI, body mass index; ITT, intent to treat; SD, Standard Deviation; VVC, vulvovaginal candidiasis

[Table 11](#) summarizes key baseline (after induction treatment) signs and symptoms and microbiologic characteristics of the ITT population. Nearly 100% of participants in each treatment arm had a baseline signs and symptoms score of 0 to 2, consistent with study eligibility criteria. There was a slight imbalance within the 0 to 2 range with more placebo subjects having with a score of 0 at baseline.

Most participants did not grow *Candida* pathogens at baseline and had negative baseline screening cultures (84.3% and 81.7%, respectively). The most frequently cultured *Candida spp.* among subjects with positive cultures at baseline were *C. albicans* (8.3% and 6.4%, oteseconazole and placebo arms, respectively) and *C. glabrata* (3.7% and 6.4%, oteseconazole and placebo arms, respectively).

Table 11. Trial CL-011 Baseline Signs and Symptoms and Microbiologic Characteristics, ITT Population

Characteristics	Oteseconazole (N=217)	Placebo (N=109)	Total (N=326)
Baseline signs and symptoms score			
Mean (SD)	0.7 (0.85)	0.4 (0.70)	0.6 (0.81)
Median (min, max)	0.0 (0, 4)	0.0 (0, 2)	0.0 (0, 4)
Baseline signs and symptoms score, by category			
0-2	215 (99.1)	109 (100.0)	324 (99.4)
0	119 (54.8)	75 (68.8)	194 (59.5)
1	51 (23.5)	21 (19.3)	72 (22.1)
2	45 (20.7)	13 (11.9)	58 (17.8)
3	1 (0.5)	0	1 (0.3)
4-8	1 (0.5)	0	1 (0.3)

Characteristics	Oteseconazole (N=217)	Placebo (N=109)	Total (N=326)
Culture results at baseline			
Negative for <i>Candida</i>	183 (84.3)	89 (81.7)	272 (83.4)
Positive for <i>Candida</i>	29 (13.4)	17 (15.6)	46 (14.1)
Missing/Unknown	5 (2.3)	3 (2.8)	8 (2.5)
Pathogen at baseline			
Of those positive for <i>Candida</i>			
<i>Candida albicans</i>	18 (8.3)	7 (6.4)	25 (7.7)
<i>Candida glabrata</i>	8 (3.7)	7 (6.4)	15 (4.6)
<i>Candida parapsilosis</i>	2 (0.9)	0	2 (0.6)
<i>Candida tropicalis</i>	1 (0.5)	0	1 (0.3)
<i>Candida dubliniensis</i>	0	1 (0.9)	1 (0.3)
<i>Candida krusei</i>	0	1 (0.9)	1 (0.3)
<i>Candida spp.</i>	0	1 (0.9)	1 (0.3)
Of those negative for <i>Candida</i>			
<i>Saccharomyces cerevisiae</i>	2 (0.9)	2 (1.8)	4 (1.2)
<i>Cryptococcus albidus</i>	1 (0.5)	0	1 (0.3)
<i>Cryptococcus albidus, Rhodotorula glutinis/Rhodotorula mucilaginosa</i>	1 (0.5)	0	1 (0.3)
<i>Rhodotorula glutinis/Rhodotorula mucilaginosa</i>	1 (0.5)	0	1 (0.3)
Yeast	1 (0.5)	0	1 (0.3)

Source: Reviewer verified numbers in the Table using ADSL dataset
Abbreviations: ITT, intent to treat.

The use of any concomitant medication was 175 (81%) in oteseconazole and 85 (78%) in placebo subjects in the safety population. The most frequently used concomitant medications were paracetamol (10% in oteseconazole and 14% in placebo) and levonorgestrel (12% in oteseconazole and 9% in placebo). Note that fluconazole was not considered a concomitant medication in the study report since the use of fluconazole was allowed per the protocol for the treatment of an episode VVC during the study. However, fluconazole was used by 57 (26%) subjects who received oteseconazole and 54 (50%) subjects who received placebo.

6.2.1.4.1. Efficacy Results

The proportion of subjects with ≥ 1 culture-verified acute VVC episodes during the maintenance phase (post randomization through Week 48) in the ITT population was the primary endpoint, and the results are summarized in [Table 12](#).

The number of subjects with ≥ 1 culture-verified acute VVC episodes through Week 48 was 14 subjects in oteseconazole and 45 subjects in placebo. A total of 53 subjects, 42 from oteseconazole and 11 from placebo, did not have complete follow-up. Results of analysis using two methods for handling this lack of complete follow-up are presented in [Table 12](#). The primary method used multiple imputation, and a second method imputed all subjects with missing data as recurrences. Both methods indicated the proportion of subjects with ≥ 1 culture-verified acute VVC episodes through Week 48 were statistically significantly lower in the oteseconazole arm than in the placebo arm ($p < 0.001$). The average percentage of subjects with ≥ 1 culture-verified acute VVC episode through Week 48 was 6.7% in oteseconazole and 42.8% in placebo using the multiple imputation (MI) method. In the analysis in which missing data were counted as failures, the estimated percentages were 25.8% for oteseconazole and 51.4% for placebo.

Table 12. Proportion of Subjects ≥ 1 Culture-Verified Acute VVC Episodes During Maintenance Phase (by Week 48) for Trial CL-011: ITT Population

Variable	Oteseconazole N=217 n (%)	Placebo N=109 n (%)
Recurrence	14 (6.5)	45 (41.3)
No documented recurrence	203 (93.5)	64 (58.7)
Full-follow-up with no recurrence	161 (74.2)	53 (48.6)
Incomplete follow-up	42 (19.4)	11 (10.1)
Analysis method		
Multiple imputation, average % ^[1]	6.7	42.8
Min, max (%)	(6.5, 7.4)	(41.3, 45.0)
P-value	<0.0001	
Missing as failures ^[2]	56 (25.8)	56 (51.4)
P-value ^[3]	<0.0001	

Source: Adapted from Table 14.2.1.1 and Table 14.2.1.5 and conducted analyses by reviewer using ADEFF dataset

^[1] Subjects with incomplete follow-up had their missing value imputed using a multiple imputation method

^[2] Subjects with incomplete follow-up had their missing values imputed as failures.

^[3] Chi-square test comparing active treatment to placebo

Abbreviations: ITT, intent to treat, VVC, vulvovaginal candidiasis.

The results of time to first recurrence of culture-verified acute VVC infection are summarized in [Table 13](#) and presented in the Kaplan Meier plot in [Figure 2](#). The hazard ratio was 0.11 ($p < 0.001$), and oteseconazole demonstrated superiority to placebo in time to first recurrence of a culture-verified acute VVC infection. Subjects with incomplete follow-up were censored at their last follow-up time in this analysis. Both treatment groups' median time to first recurrence of a culture-verified acute VVC episode were not reached because less than 50% of subjects had recurrence events during the study. When considering the timing of the events, more recurrence events through Week 12 occurred in the placebo arm (26 (23.9%)) than in the oteseconazole arm (4 (1.8%)). After treatment through Week 48, 10 recurrence events (4.6%) occurred in the oteseconazole arm and 19 recurrence events (17.4%) occurred in the placebo arm.

Table 13. Time to First Recurrence of a Culture-Verified Acute VVC Episode Through Week 48 for Trial CL-011: ITT Population

Analysis Method	Oteseconazole N=217 n (%)	Placebo N=109 n (%)
Actual known recurrence	14 (6.5)	45 (41.3)
Recurrence by Week 12	4 (1.8)	26 (23.9)
Week 12 to End of Study	10 (4.6)	19 (17.4)
P-value*	<0.001	
Hazard ratio (95%CI)	0.11 (0.06, 0.21)	
P-value [#]	<0.001	

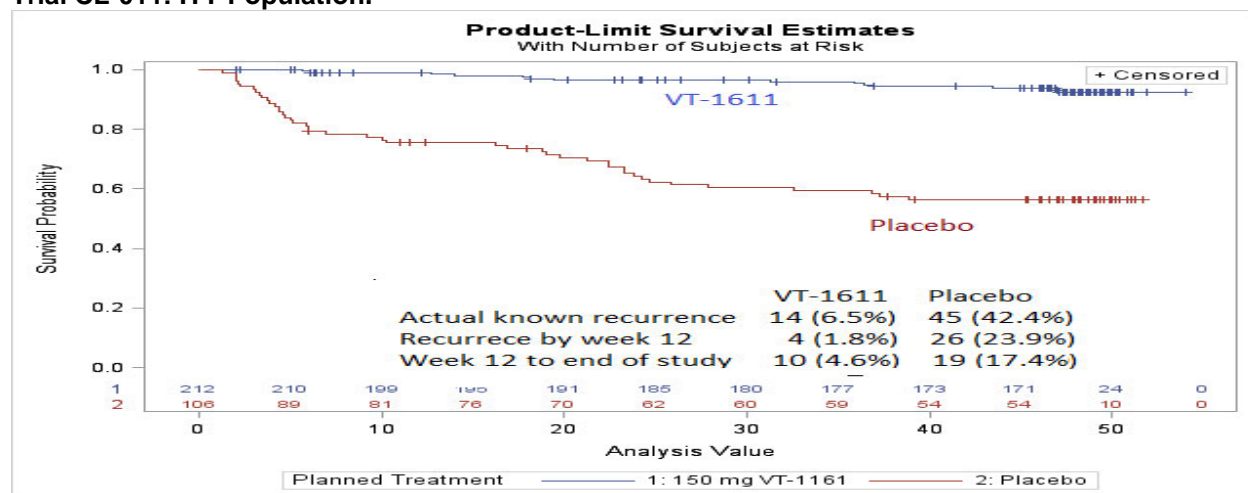
Source: Adapted from Table 14.2.1.1 and conducted analyses by reviewer using ADTTE dataset

* Log-rank test comparing active treatment to placebo

[#] Chi-square test

Abbreviations: ITT, intent to treat, VVC, vulvovaginal candidiasis.

Figure 2. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-011: ITT Population.



Source: Adapted from Figure 14.4.4.1.2 and conducted analyses by reviewer using ADTTE dataset
VT-1161=oteseconazole
Abbreviations: ITT, intent to treat, VVC, vulvovaginal candidiasis.

Results of analyses of the additional secondary endpoints are reported in Section 17. Note that the results of the additional analyses of the recurrent cases of VVC were consistent with these results shown above. However, no effect was seen with the endpoints of SF-36 MCS or the patient reported outcome survey total score.

6.2.2. Trial CL-012

6.2.2.1. Design, Trial CL-012

Trial CL-012 was a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of oteseconazole oral capsules in the treatment of subjects with RVVC. Its design was identical to CL-011. Refer to 6.2.1.1 for details. The full protocol synopsis is contained in Section 15.1 of this review.

This study design supported the indication of reducing the incidence of recurrence of VVC.

6.2.2.2. Eligibility Criteria, Trial CL-012

The inclusion and exclusion criteria were the same as study CL-011. Refer to Section 6.2.1.2.

6.2.2.3. Statistical Analysis Plan, Trial CL-012

The statistical methods were the same as Study CL-011. Refer to 6.2.1.3.

6.2.2.4. Results of Analyses, Trial CL-012

Subject Disposition, Demographics and Baseline Characteristics

The study was conducted at 84 sites in North America (United States and Canada) and Europe (Belgium, Czech Republic, Hungary, Romania, and Ukraine). The first patient was enrolled on October 4, 2018, and the study was completed on October 13, 2020.

A total of 534 subjects were screened and of those, 425 subjects were entered into the induction phase. Following the induction phase, 330 subjects were entered into the maintenance phase and

were randomized in a 2:1 ratio, with 220 subjects into oteseconazole and 110 subjects into placebo. Three subjects in the oteseconazole arm were not treated. Site 31-240 was found to have good clinical practice violations and had randomized two subjects to each treatment group prior to being shut down by the Applicant. Subjects from this site were excluded from the ITT population but were included in the safety population. The safety population therefore included 327 subjects: 217 subjects in the oteseconazole arm and 110 subjects in the placebo arm. The ITT population included 326 subjects: 218 subjects in the oteseconazole arm and 108 subjects in the placebo arm. Subjects' screening and randomization are summarized in [Table 14](#).

Table 14. Subjects' Screening and Randomization, Trial CL-012

Disposition	N
No. patients screened	534
Entered Induction Phase	425
No. patients not randomized	95
No. patients randomized	330
No. patients not treated	3

Source: Reviewer conducted analysis using ADSL dataset

Subject disposition is summarized in [Table 15](#). Of the 326 subjects in the ITT population, 27 (12.3%) of 218 oteseconazole subjects and 11 (10%) of 108 placebo subjects were discontinued from the study. The most common reasons for discontinuation were withdrawal of consent (6.7%) and lost to follow-up (2.1%). The mean number of days (SD) of maintenance treatment in the ITT population was 80 (17.0) in the oteseconazole arm and 78 (20.5) in the placebo arm. Treatment compliance was high in both treatment arms. Daily compliance (defined as the number of doses taken divided by 7) during the daily dosing phase had a mean (SD) of 98.6 (11.7) for oteseconazole and 99.1% (8.3) for placebo. Compliance for the weekly dosing phase (number of doses divided by 11) was 91.7% (24.3) and 90.1% (26.1) for oteseconazole and placebo, respectively. The amount of follow-up was comparable for the two treatment arms with a mean follow-up time for oteseconazole subjects of 310 days and 303 days for placebo.

Table 15. Patient Disposition, Trial CL-012

	Oteseconazole N=220 n (%)	Placebo N=110 n (%)	Total N=330 n (%)
Randomized Population			
Intent-to-treat population	218 (99.1)	108 (98.2)	326 (98.8)
Safety population	217 (98.6)	110 (100)	327 (99.1)
Completed treatment	153 (69.5)	82 (74.5)	235 (72.1)
Completed study	191 (86.8)	91 (84.3)	282 (85.5)
Discontinued study	27 (12.3)	11 (10)	38 (17.4)
Adverse event	1 (<1)	0 (0)	1 (<1)
Pregnancy	1 (<1)	0 (0)	1 (<1)
Lost to follow-up	6 (2.8)	1 (<1)	7 (2.1)
Withdrawal by subject	15 (6.9)	7 (6.4)	22 (6.7)
Sponsor request	1 (<1)	0 (0)	1 (<1)
Other	0 (0)	1 (<1)	1 (<1)
Noncompliance	0	2 (1.8)	2 (<1)
Investigator discretion	2 (<1)	1 (<1)	3 (<1)
Lab revealed clinically significant changes	1 (<1)	0 (0)	1 (<1)

Source: Reviewer conducted analysis using ADSL dataset

Abbreviations: N, number of subjects; n, number of subjects with at least one event

Demographic and baseline characteristics, which were similar between the arms, are summarized for the ITT population in [Table 16](#). The mean age was 34 years old. No participants were younger than 18 years old and a single participant, randomized to the placebo arm, was older than 65. A majority was White (88.7%) and Not Hispanic or Latino (85%). Thirty-six percent of subjects were from the United States.

Table 16. Demographic and Baseline Characteristics for Trial CL-012: ITT Population

Characteristic	Oteseconazole N=218 n (%)	Placebo N=108 n (%)	Total N=326 n (%)
Age group, years, n (%)			
Mean (SD)	34 (9.4)	36 (10.8)	34 (9.9)
Median (Min, Max)	33 (18, 61)	34 (18, 73)	33 (18, 73)
18-33	111 (50.9)	54 (50.0)	165 (50.6)
≥34	107 (49.1)	54 (50.0)	161 (49.4)
Sex			
Female	218 (100)	108 (100)	326 (100)
Race, n (%)			
Black or African American	23 (10.6)	8 (7.4)	31 (9.5)
Other	2 (<1)	4 (3.7)	6 (1.8)
White	193 (88.5)	96 (88.9)	289 (88.7)
Ethnicity, n (%)			
Hispanic or Latino	30 (13.8)	18 (16.7)	48 (14.7)
Not Hispanic or Latino	187 (85.8)	90 (83.3)	277 (85.0)
Unknown	1 (<1)	0	1 (<1)
Country of participation, n (%)			
Belgium	18 (8.3)	8 (7.4)	26 (8.0)
Czech	51 (23.4)	22 (20.4)	73 (22.4)
Hungary	8 (3.7)	3 (2.8)	11 (3.4)
Romania	44 (20.2)	28 (25.9)	72 (22.1)
Ukraine	17 (7.8)	9 (8.3)	26 (8.0)
United States	80 (36.7)	38 (35.2)	118 (36.2)
Region			
Europe	138 (63.3)	70 (64.8)	208 (63.8)
North America	80 (36.7)	38 (35.2)	118 (36.2)
BMI (kg/m ²)			
Mean (SD)	24.8 (5.8)	24.5 (5.3)	24.7 (5.7)
Diabetes mellitus	5 (2.3)	1 (<1)	6 (1.8)
Acute VVC episode in past 12 months			
Mean (SD)	4.3 (2.4)	4.4 (2.0)	4.3 (2.3)
<4	108 (49.5)	48 (44.4)	156 (47.9)
≥4	110 (50.5)	60 (55.6)	170 (52.1)

Source: Adapted Table 14.1.2.1 and reviewer conducted analyses using ADSL
Abbreviations: BMI, Body mass index; ITT, intent-to-treat; VVC, vulvovaginal candidiasis

[Table 17](#) summarizes key baseline (after induction treatment) signs and symptoms and microbiologic characteristics of the ITT population. Nearly 100% of participants in each treatment arm had a baseline signs and symptoms score of 0 to 2, consistent with study eligibility criteria.

Most participants did not grow *Candida* pathogens at baseline and had negative baseline screening cultures (86.2 and 83.3%, respectively). The most frequently cultured *Candida spp.* among subjects with positive cultures at baseline were *C. albicans* (5.5% oteseconazole and 8.3% placebo).

Table 17. Trial CL-012 Baseline Microbiologic Characteristics, ITT Population

Characteristics	Oteseconazole (N=218)	Placebo (N=108)	Total (N=326)
Baseline signs and symptoms score			
Mean (SD)	0.6 (0.80)	0.6 (0.79)	0.6 (0.80)
Median (min, max)	0.0 (0, 4)	0.0 (0, 2)	0.0 (0, 4)
Baseline signs and symptoms score, by category			
0-2	216 (99.1)	108 (100.0)	324 (99.4)
0	123 (56.4)	59 (54.6)	182 (55.8)
1	58 (26.6)	28 (25.9)	86 (26.4)
2	35 (16.1)	21 (19.4)	56 (17.2)
3	1 (0.5)	0	1 (0.3)
4-8	1 (0.5)	0	1 (0.3)
Culture results at baseline			
Negative for <i>Candida</i>	188 (86.2)	90 (83.3)	278 (85.3)
Positive for <i>Candida</i>	20 (9.2)	17 (15.7)	37 (11.3)
Missing information	10 (4.6)	1(0.9)	11 (3.4)
Pathogen at baseline			
Of those positive for <i>Candida</i>			
<i>Candida albicans</i>	12 (5.5)	9 (8.3)	21 (6.4)
<i>Candida glabrata</i>	3 (1.4)	5 (4.6)	8 (2.5)
<i>Candida parapsilosis</i>	3 (1.4)	2 (1.9)	5 (1.5)
<i>Candida krusei</i>	1 (0.5)	1 (0.9)	2 (0.6)
<i>Candida glabrata, Candida tropicalis</i>	1 (0.5)	0	1 (0.3)
Of those negative for <i>Candida</i>			
<i>Saccharomyces cerevisiae</i>	2 (0.9)	1 (0.9)	3 (0.9)
<i>Cryptococcus albidus, Saccharomyces cerevisiae</i>	1 (0.5)	0	1 (0.3)
Yeast	1 (0.5)	0	1 (0.3)
<i>Rhodotorula glutinis/Rhodotorula mucilaginosa</i>	0	1 (0.9)	1 (0.3)

Source: Reviewer conducted analysis using ADSL
Abbreviations: ITT, intent to treat.

The use of any concomitant medication was 179 (82%) in the oteseconazole subjects and 95 (86%) in the placebo subjects in the safety population. The most frequently used concomitant medications were ibuprofen (38 subjects [12%]), levonorgestrel (36 subjects [11%]), and drospirenone/ethinylestradiol (28 subjects [8%]). As in Study 011, fluconazole was not considered a concomitant medication by the Applicant in the study report. However, 46 (21%) oteseconazole subjects and 50 (46%) placebo subjects received fluconazole.

6.2.2.4.1. Efficacy Results

The proportion of subjects with ≥ 1 culture-verified acute VVC episode during the maintenance phase (post randomization through Week 48) in the ITT population was the primary endpoint and the results are summarized in [Table 18](#).

Eight subjects in the oteseconazole arm and 39 subjects in the placebo arm had ≥ 1 culture-verified acute VVC episode through Week 48. A total of 51 subjects, 38 on oteseconazole and 13 on placebo had incomplete follow-up. Results of analyses using two methods for handling this lack of complete follow-up are presented in [Table 18](#). The primary method used multiple imputation, and a second method imputed all subjects with missing data as recurrences. Both methods resulted in statistically significantly lower rates of recurrences in the oteseconazole arm

than in the placebo arm ($p < 0.001$). The average percentage of subjects with ≥ 1 culture-verified acute VVC episode through Week 48 was 3.9% in the oteseconazole arm and 39.4% in the placebo arm using the MI method. The analysis method in which missing data were imputed as failures led to 46 (21.1%) subjects in the oteseconazole arm and 52 (48.1%) in the placebo arm with least one culture-verified acute VVC episode.

Table 18. Proportion of Subjects ≥ 1 Culture-Verified Acute VVC Episodes During Maintenance Phase for Trial CL-012: ITT Population

	Oteseconazole N=218 n (%)	Placebo N=108 n (%)
Analysis Method		
Recurrence	8 (3.7)	39 (36.1)
No documented recurrence	210 (96.3)	69 (63.9)
Full follow-up with no recurrence	172 (78.9)	56 (51.9)
Incomplete follow-up	38 (17.4)	13 (12.0)
Analysis method		
Multiple imputation, average % ^[1]	3.9	39.4
Min, max (%)	3.7, 4.6	38.0, 42.6
P-value	< 0.001	
Missing as failures ^[2]	46 (21.1)	52 (48.1)
P-value ^[3]	< 0.001	

Source: Adapted from Table 14.2.1.1 and Table 14.2.1.5 of and confirmed by reviewer using ADEFF dataset

^[1]: Subjects with incomplete follow-up had their missing value imputed using a multiple imputation method

^[2]: Subjects with incomplete follow-up had their missing values imputed as failures.

^[3]: Chi-square test comparing active treatment to placebo

Abbreviations: ITT, intent to treat; VVC, vulvovaginal candidiasis.

The results of time to first recurrence of culture-verified acute VVC infection are summarized in [Table 19](#) and presented in the Kaplan Meier plot in [Figure 3](#). The hazard ratio was 0.08 ($p < 0.001$), and oteseconazole demonstrated superiority to placebo in time to first recurrence of verified acute VVC infection. Subjects with incomplete follow-up were censored at their last follow-up time in this analysis. Both treatment groups' median time to first recurrence of a culture-verified acute VVC episode was not reached because less than 50% of subjects had recurrence events during the study. When considering the timing of the events, there were more recurrences through Week 12 in the placebo arm (28 (25.9%)) compared to the oteseconazole arm (4 (1.8%)). After treatment through Week 48, there were 4 (1.8%) recurrence events in the oteseconazole arm and 11 (10.1%) recurrence events in the placebo arm.

Table 19. Time to First Recurrence of a Culture-Verified Acute VVC Episode for Trial CL-012: ITT Population

	Oteseconazole N=218 n (%)	Placebo N=108 n (%)
Analysis Method		
Actual known recurrence	8 (3.7)	39 (36.1)
Recurrence by Week 12	4 (1.8)	28 (25.9)
Week 12 to end of study	4 (1.8)	11 (10.1)
P-value ^[1]	< 0.001	
Hazard's ratio (95%CI)	0.08 (0.04, 0.17)	
P-value ^[2]	< 0.001	

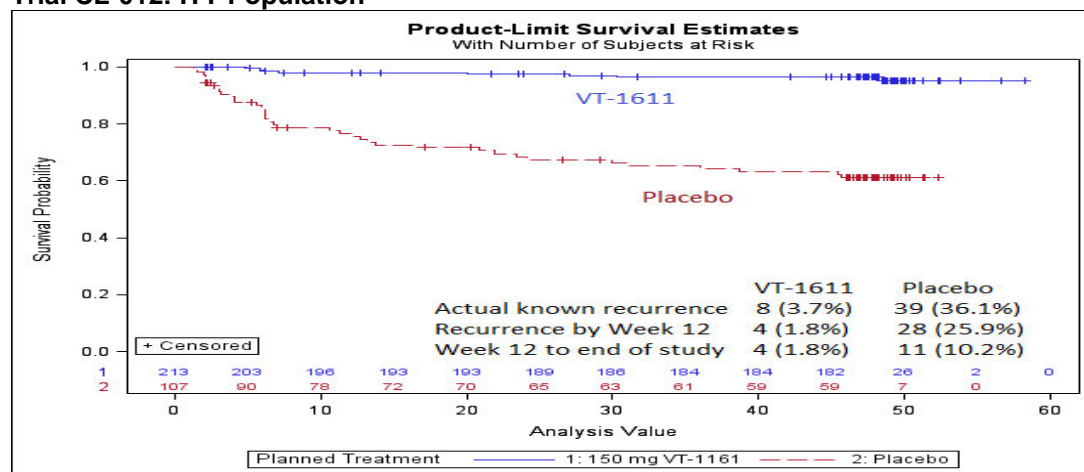
Source: Adapted from Table 14.2.1.1 and conducted analyses by reviewer using ADTTE dataset

^[1] Log-rank test comparing active treatment to placebo

^[2] Chi-square test

Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

Figure 3. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-012: ITT Population



Source: Reviewer conducted analysis using ADTTE dataset
 VT-1161=oteseconazole
 Abbreviations: ITT, intent to treat; VVC, vulvovaginal candidiasis.

Results of analyses of the additional secondary endpoints are reported in Section 17. Note that the results of the additional analyses of the recurrent cases of VVC were consistent with these results shown above. However, no effect was seen with the endpoints of SF-36 MCS or the patient-reported outcome survey total score.

6.2.3. Trial CL-017

6.2.3.1. Design, Trial CL-017

Trial CL-017 was a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study conducted to evaluate the safety and efficacy of oteseconazole capsules versus fluconazole followed by placebo in the treatment and prevention of recurrence of acute, symptomatic VVC episodes in females with a history of RVVC. See Section 15 for the full protocol synopsis of this study.

Trial CL-017 was divided into a 2-week induction phase, an 11-week maintenance phase, and a 37-week follow-up period. Unlike Trials CL-011 and CL-012, participants in Trial CL-017 were randomized at the start of the induction phase. Subjects were randomized in a 2:1 ratio to one of the following two treatment arms:

- Oteseconazole arm:
 - Induction phase: 600 mg oteseconazole (4x150 mg capsules) on Day 1 and 450 mg oteseconazole (3x150 mg capsules) on Day 2 and;
 - Maintenance phase: 150 mg Oteseconazole weekly for 11 weeks starting on Day 14
- Fluconazole/Placebo arm:
 - Induction phase: 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole
 - Maintenance phase: placebo weekly for 11 weeks

Blinding was maintained with the use of a double-dummy design.

Eligible subjects were randomized and entered the induction phase. During the induction phase, subjects presenting with an acute VVC infection were treated with either oteseconazole or fluconazole. Subjects returned approximately 14 days after the first dose of oteseconazole or fluconazole for evaluation. If the acute VVC infection had resolved (defined by a signs and symptoms score of <3), they entered the maintenance phase to continue onto their assigned treatment of either oteseconazole or a matching placebo regimen. If the acute VVC infection had not resolved, the subject was considered an induction failure and was to be carried forward as a failure for the primary analysis. Each participant was anticipated to remain in the study for approximately 50 weeks.

Similar to CL-011 and CL-012, CL-017 supports an indication for reducing the incidence of recurrent VVC.

(b) (4)

(b) (4)

6.2.3.2. Eligibility Criteria, Trial CL-017

Eligible subjects included generally healthy postmenarchal, nonpregnant females ≥ 12 years of age with an acute VVC infection and a history of RVVC, defined as:

- Three or more patient-reported and/or laboratory-confirmed episodes of acute VVC in the past 12 months including the episode confirmed at screening
- At least one episode (not including the current episode) documented by a positive culture, polymerase chain reaction, Affirm test, KOH test, or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.

Study exclusions were similar to Trials CL-011 and CL-012. Subjects were ineligible for study participation if, at screening or on Day 1, they were noted to have the following key exclusion criteria:

- Concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*)
- An active human papillomavirus infection, as evidenced by visible condylomas on vulvovaginal examination at screening and Day 1

- The presence or a history of another vaginal or vulvar condition(s) that in the investigator's opinion would have confounded the interpretation of clinical response
- Use of any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to screening or used topical vulvar or vaginal steroids during the study or within 7 days prior to screening
- A laboratory abnormality that in the opinion of the investigator was likely to introduce additional risk to the subject or might interfere with data interpretation.

Females were also excluded from study participation if they:

- Were found to be pregnant at screening
- Had active substance abuse
- Had uncontrolled diabetes mellitus
- Had a history of or an active cervical/vaginal cancer

Females of child-bearing potential were instructed to use appropriate contraceptive method(s) throughout the study.

6.2.3.3. Statistical Analysis Plan, Trial CL-017

The primary efficacy outcome measure was the proportion of subjects with one or more culture-verified acute VVC episodes (postrandomization through Week 50) in the ITT population, which included the subjects who failed clearing their infection during the induction phase. An acute VVC episode (considered a recurrent episode) was defined as a positive culture for *Candida* species and a clinical signs and symptoms score of ≥ 3 .

Note that the phrase "which included the subjects who failed clearing their infection during the induction phase" was interpreted by the Agency to mean that subjects who failed clearing their initial infection would be carried forward as failures for the primary endpoint. This was important because subjects were randomized at the time of the initial episode such that effect on that episode was directly related to the treatment effect. This was discussed with the Applicant at the design stage of the trial. Therefore, for clarity, we interpreted the primary endpoint to be defined as the occurrence of either a failure of the initial treatment of the presenting VVC episode during the induction phase or the development of one or more culture-verified acute VVC episodes during the maintenance phase (postrandomization through Week 50) in the ITT population.

As with Trials CL-011 and -012, subjects who may have been treated with additional VVC medication during the study were not automatically considered as having a recurrent episode. This will be addressed in Section [6.3.1](#).

Key secondary endpoints include the following:

- Proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of < 3) at Day 14 following treatment with oteseconazole or fluconazole in the ITT population
- Proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms score of ≥ 3 during the maintenance phase (post-Day 14 through Week 50) in the ITT population
- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms of ≥ 3 during the maintenance phase in the ITT population

- Proportion of subjects with at least one positive culture for *Candida* species during the maintenance phase in the ITT population

The hierarchical/gatekeeping method was used to control for the type I error rate at 0.05 for multiplicity of secondary endpoints. The protocol specified that the first secondary endpoint would be tested using a noninferiority hypothesis rather than superiority.

The primary method of analysis was a comparison of the proportions of subjects with either a failure of the initial treatment of the presenting VVC episode during the induction phase or the development of one or more culture-verified acute VVC episodes during the maintenance phase through Week 50 using a chi-square test for test arm versus the control based on the ITT population which included all randomized subjects.



(b) (4) Note that the study report included an “induction modified intent-to-treat population” (induction modified intent-to-treat [mITT]) defined as all randomized subjects who had a positive central KOH test at screening and a positive culture at screening. This definition is more in line with the primary analysis population recommended in the FDA VVC guidance document (August 2019) and will be the population used in this review when discussing the Day 14 results.

Time to recurrence of an acute VVC episode was estimated using the Kaplan-Meier method. Subjects who failed to clear their acute infection during the induction phase were excluded from these analyses. A chi-square test was used to compare the active treatment group to the placebo group for each key secondary endpoint that was a proportion.

For handling subjects with missing data, the primary analysis approach imputed missing values using a multiple imputation approach. This was used for both intermittent missing data, i.e., when a subject had a missed visit or a missed assessment of signs and symptoms or missing culture results, or if a subject has terminal missing data, i.e., if a subject discontinues from the trial. The missing values were imputed using baseline information of region, treatment, baseline BMI, baseline age, ethnicity and visit. Additional details of the multiple imputation methods are the same as those used for trial CL-011.

Additionally, sensitivity analyses were conducted using different methods for handling missing data. One method treats subjects with missing data as having had a recurrence. The analysis of time to recurrence censors subjects who discontinue the study.

Assuming a treatment difference in subjects with one or more culture-verified acute VVC episodes during the maintenance phase (postrandomization through Week 50) of 35% between oteseconazole and placebo, a sample size of 82 active subjects and 41 placebo subjects provided at least 90% power with a 50% recurrence rate for fluconazole/placebo. For the first key secondary endpoint, the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with oteseconazole or fluconazole, a sample size of 120 subjects in the oteseconazole arm and 60 subjects in the fluconazole/placebo arm provided at least 88% power to detect noninferiority between the treatment groups with a

noninferiority margin of 15% and a type 1 error rate of 0.05. Therefore, the study planned to enroll 180 total subjects, including 120 subjects in the oteseconazole arm and 60 subjects in the fluconazole/placebo arm.

6.2.3.4. Results of Analyses, Trial CL-017

Subject Disposition, Demographics and Baseline Characteristics

The study was conducted at 84 sites in the United States. The first patient was enrolled on October 14, 2018, and the study was completed on October 13, 2020.

The subjects' screening and randomization information is summarized in [Table 20](#). A total of 251 subjects were screened, and 219 subjects were entered into the induction phase and randomized with a 2:1 ratio, resulting in 147 oteseconazole subjects and 72 fluconazole/placebo subjects. All subjects were treated and received the treatment they were randomized to with the exception of one subject randomized to oteseconazole who was not treated.

Table 20. Subjects' Screening and Randomization, Trial CL-017

Disposition	N
No. patients screened	251
Entered induction phase	219
No. patients not randomized	36
No. patients randomized	219
No. patients not treated	1

Source: Reviewer conducted analysis using ADSL dataset

The subjects' disposition is summarized [Table 21](#). The ITT population included 219 subjects: 147 subjects in the oteseconazole arm and 72 subjects in the fluconazole/placebo arm. The safety population, which included all randomized and treated subjects, included 218 subjects: 146 subjects in the oteseconazole arm and 72 subjects in the fluconazole/placebo arm. The induction mITT population included 81 (55.2%) oteseconazole subjects and 38 (52.8%) fluconazole/placebo subjects. Subjects excluded from the induction mITT population included 118 subjects (80 oteseconazole and 38 fluconazole/placebo) who did not have a positive culture at screening and 1 oteseconazole subject who did not have a positive KOH at screening.

The subjects who completed the study included 112 (76.2%) oteseconazole subjects and 55 (76.4%) fluconazole/placebo subjects. The most common reasons for discontinuation were due to induction failure (14.2%) and lost to follow-up (5.0%). The mean overall follow-up time for oteseconazole was 293 days and 295 days for fluconazole/placebo.

Table 21. Subject Disposition, Trial CL-017

	Drug Dosage 1 N=147 n (%)	Placebo N=72 n (%)	Total N=219 n (%)
Randomized Population			
Intent-to-treat population (ITT)	147 (100)	72 (100)	219 (100)
Safety population	146 (98.6)	72 (100)	327 (99.1)
Induction mITT population	66 (44.9)	34 (47.2)	100 (45.7)
Completed treatment	112 (76.2)	55 (76.4)	167 (76.3)
Completed study	112 (76.2)	55 (76.4)	167 (76.3)
Discontinued study	35 (12.3)	17 (23.6)	38 (17.4)
Induction failure	22 (15.0)	9 (12.5)	31 (14.2)
Lost to follow-up	5 (3.4)	6 (8.3)	11 (5.0)
Withdrawal by subject	4 (2.7)	1 (1.4)	5 (2.3)
Other	1 (<1)	1 (1.4)	2 (<1)
Screen failure	1 (<1)	0 (0)	1 (<1)
Adverse event	1 (<1)	0 (0)	1 (<1)
Sponsor request	1 (<1)	0 (0)	1 (<1)

Source: Reviewer conducted analysis using ADSL dataset
Abbreviations: ITT, intent to treat; mITT, modified intent to treat.

Demographic and baseline characteristics for the ITT population are summarized in [Table 22](#). The subjects' demographic and baseline characteristics were comparable between arms. The mean age was 34 years old. Two subjects, one in each treatment arm, were <18 years old; whereas, two subjects, one in each treatment arm, were ≥65-years old. Most of the subjects were White (59%). Twenty-six percent of all subjects were Latinos, the majority of whom identified as White. Over 80% of subjects in the ITT population had between three to six acute VVC episodes in the 12 months prior to the study.

Table 22. Subjects' Demographic and Baseline Characteristics for Trial CL-017: ITT Population

Characteristic	Oteseconazole N=147 n (%)	Fluconazole/Placebo N=72 n (%)	Total N=219 n (%)
Age group, years, n (%)			
Mean (SD)	34 (10.7)	36 (11.7)	35 (11.0)
Median (min, max)	34 (16, 66)	36 (16, 78)	34 (16, 78)
12-17	1 (<1)	1 (1.4)	2 (<1)
18-33	72 (49.0)	30 (41.7)	102 (46.6)
≥34	74 (50.3)	41 (56.9)	115 (52.5)
Sex			
Female	147 (100)	72 (100)	219 (100)
Race, n (%)			
Black or African American	47 (32.0)	27 (37.5)	74 (33.8)
Other	12 (8.2)	3 (4.2)	15 (6.8)
White	88 (59.9)	42 (58.3)	130 (59.4)
Ethnicity, n (%)			
Hispanic or Latino	38 (25.9)	19 (26.4)	57 (26.0)
Not Hispanic or Latino	109 (74.2)	53 (73.6)	162 (74.0)
Country of participation, n (%)			
United States	147 (100)	147 (100)	217 (100)
BMI (kg/m²)			
Mean (SD)	24.8 (5.8)	24.5 (5.3)	24.7 (5.7)
Diabetes mellitus	11 (7.5)	5 (6.9)	16 (7.3)

Characteristic	Oteseconazole N=147 n (%)	Fluconazole/Placebo N=72 n (%)	Total N=219 n (%)
Acute VVC episode in past 12 months			
Mean (SD)	4.7 (2.8)	4.7 (2.5)	4.7 (2.7)
Median (min, max)	4 (3, 20)	4 (3, 13)	4 (3, 20)
<4	69 (46.9)	34 (47.2)	103 (47.0)
≥4	78 (53.1)	38 (52.8)	116 (53.0)

Source: Reviewer conducted analysis using ADSL dataset

Abbreviations: BMI, Body mass index; ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

A summary of signs and symptoms and key baseline microbiologic characteristics in the ITT population is summarized in [Table 23](#). No major imbalances were observed between treatment groups. Fifty-three percent of all participants in the ITT population had a negative *Candida* culture at baseline, though all but one subject had a positive KOH smear. *Candida albicans* was the most frequently cultured baseline pathogen across both treatments. Six subjects (2.7%), four in the oteseconazole arm and two in the placebo arm, were noted to have baseline mixed *Candida* infections. Baseline mean and median signs and symptom scores in both treatment arms were 8.0 and 7.0, respectively. In all, 85.4% of subjects had signs and symptom scores of between 3 to 6 and 7 to 9.

Table 23. Trial CL-017 Baseline Signs/Symptoms and Microbiologic Characteristics, ITT Population

Characteristic	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)	Total (N=219)
Baseline (Day 1) culture result			
Negative for <i>Candida</i>	78 (53.1)	38 (52.8)	116 (53.0)
Positive for <i>Candida</i>	67 (45.6)	34 (47.2)	101 (46.1)
Missing/Unknown	2 (1.4)	0	2 (0.9)
Baseline (Day 1) pathogen			
Of those positive for <i>Candida</i>			
<i>Candida albicans</i>	61 (41.5)	27 (37.5)	88 (40.2)
<i>Candida albicans, Candida glabrata</i>	2 (1.4)	2 (2.8)	4 (1.8)
<i>Candida albicans, Candida parapsilosis</i>	1 (0.7)	0 (0.0)	1 (0.5)
<i>Candida glabrata</i>	1 (0.7)	3 (4.2)	4 (1.8)
<i>Candida glabrata, Candida krusei</i>	1 (0.7)	0 (0.0)	1 (0.5)
<i>Candida tropicalis</i>	1 (0.7)	1 (1.4)	2 (0.9)
<i>Candida parapsilosis</i>	0 (0.0)	1 (1.4)	1 (0.5)
Of those negative for <i>Candida</i>			
<i>Lodderomyces elongisporus</i>	0 (0.0)	1 (1.4)	1 (0.5)
<i>Trichosporon inkin</i>	0 (0.0)	1 (1.4)	1 (0.5)
No pathogen/missing	80 (54.4)	36 (50.0)	116 (53.0)
Baseline (Day 1) signs and symptoms score			
Mean (SD)	8.0 (3.59)	8.1 (3.83)	8.0 (3.67)
Median (min, max)	7.0 (3, 18)	7.0 (3, 18)	7.0 (3, 18)
Baseline (Day 1) signs and symptoms signs, by category			
3-6	64 (43.5)	29 (40.3)	93 (42.5)
7-12	63 (42.9)	31 (43.1)	94 (42.9)
13-18	20 (13.6)	12 (16.7)	32 (14.6)

Characteristic	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)	Total (N=219)
Baseline (Day 1) KOH smear			
Positive	146 (99.3)	72 (100.0)	218 (99.5)
Missing/Unknown	1 (0.7)	0	1 (0.5)

Source: Reviewer's analysis using ADSL.xpt.

Note: *Lodderomyces elongisporus* is a member of *C. parapsilosis* complex and an uncommon cause of candidemia found most often in the immunocompromised.

Abbreviations: ITT, intent to treat; KOH, potassium hydroxide.

One hundred thirty-one (89.7%) subjects in the oteseconazole arm and 66 (91.7%) subjects in the fluconazole/placebo arm of the safety population used concomitant medications. The most frequently used concomitant medications were levonorgestrel (34 subjects [23.3%]), ibuprofen (31 subjects [21.1%]), and metronidazole (27 subjects [12%]). Fluconazole was not considered a concomitant medication in the study report. During the maintenance phase, 52 (35%) oteseconazole subjects and 30 (72%) fluconazole/placebo subjects received fluconazole as treatment for an episode of VVC.

6.2.3.4.1. Efficacy Results

The proportion of subjects who failed induction therapy or who had ≥ 1 culture-verified acute VVC episode during post randomization through Week 50 in the ITT population was the primary endpoint and the results are summarized in [Table 24](#). Oteseconazole demonstrated superiority to fluconazole/placebo in the proportion of subjects who either failed induction therapy or who had ≥ 1 culture-verified acute VVC episode through Week 50 ($p < 0.001$) regardless of the analysis method used. The average percentage of subjects with ≥ 1 culture-verified acute VVC episode through Week 50 was 10.3% in the oteseconazole arm and 42.9% in the placebo arm using the MI method. In the analysis method where missing assessments were counted as failures, 44 (29.9%) oteseconazole subjects and 40 (55.6%) placebo subjects had an event. It should be noted that two subjects in each treatment arm who failed induction therapy also had positive cultures at Day 14. While these subjects met the definition of a culture-verified acute VVC episode, they were counted as failures of induction therapy rather than known recurrence in [Table 24](#).

Table 24. Proportion of Subjects Who Failed Induction or Who had ≥ 1 Culture-Verified Acute VVC Episodes During Postrandomization Through Week 50 for Trial CL-017: ITT Population

	Oteseconazole N=147 n (%)	Fluconazole/Placebo N=72 n (%)
Analysis Methods		
Failure by Day 14 or recurrence through Week 50	14 (9.5)	27 (37.5)
Failure of induction therapy (Day 14)	10 (6.8)	3 (4.2)
Known recurrence through Week 50	4 (2.7)	24 (33.3)
Incomplete follow-up	30 (20.4)	13 (18.1)
Analysis method		
Multiple imputation (average %) ^[1]	10.3	42.9
Min, max (%)	9.5, 12.2	40.3, 45.8
P-value		<0.001
Missing as failures ^[2]	44 (29.9)	40 (55.6)
P-value ^[3]		<0.001

Source: Adapted from Table 14.2.1.1 of response dated 11/23/21 and Table 14.2.1.5 of CL-017 Study Report and confirmed by reviewer using ADEFF dataset

^[1]: Missing values were imputed with multiple imputation method

^[2]: Missing values were counted as failures

^[3]: Chi-square test comparing active treatment to placebo

Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

The proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment was a key secondary endpoint and the results for the ITT population are summarized in [Table 25](#). The average percentage of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment was 93.2% in oteseconazole and 95.8% in fluconazole/placebo using the MI method based on the ITT population. The difference between oteseconazole and fluconazole (95% CI) was -2.6% (-8.8%, 3.5%). When missing data were counted as failures, the proportions of subject with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment were 90.5% in oteseconazole and 90.3% in fluconazole/placebo with a difference (95% CI) of 0.2% (-9.2%, 9.6%) in the ITT population.

Table 25. Proportion of Subjects With Resolved Acute VVC Infections at Day 14 for Trial CL-017: ITT Population

Characteristic	Oteseconazole N=147 n (%)	Fluconazole/Placebo N=72 n (%)
Resolved VVC infection (score <3)	133 (90.5)	65 (90.3)
Unresolved VVC infection	10 (6.8)	3 (4.2)
Missing	4 (2.7)	4 (5.6)
Analysis method		
MI (average %) ^[1]	93.2	95.8
Difference (95% CI)		-2.6 (-8.8, 3.5)
Missing as failures ^[2]	133 (90.5)	65 (90.3)
Difference (95% CI)		0.2 (-9.2, 9.6)

Source: Adapted from Table 14.2.1.1 and Table 14.2.1.5 of CL-017 study report and confirmed by reviewer using ADEFF dataset

^[1]: Missing values were imputed with multiple imputation method

^[2]: Missing values were counted as failures

Abbreviations: ITT, intent-to-treat; MI, multiple imputation; VVC, vulvovaginal candidiasis.

As discussed above, the primary endpoint for assessing treatment of VVC recommended in the guidance would typically be based on clinical cure requiring the resolution of all signs and symptoms (i.e., signs and symptoms score = 0) and it would be conducted in an mITT population similar to how the induction mITT population is defined for this study. The results of this analysis are presented in [Table 26](#). The average percentage of subjects with clinical cure at Day 14 was 49.7% in oteseconazole and 35.9% in fluconazole/placebo and the 95% CI of the difference was (-6.6%, 34.2%) using the MI method for the induction mITT population. When missing data were counted as failures, the proportions of subjects with clinical cure at Day 14 were 48.5% in the oteseconazole arm and 35.3% in the fluconazole/placebo arm with a difference (95% CI) of 13.2% (-9.1%, 35.5%) for the induction mITT population.

Table 26. Proportion of Subjects With Clinical Cure at Day 14 for Trial CL-017: Induction mITT Population

Characteristic	Oteseconazole	Fluconazole/Placebo
	N=66 n (%)	N=34 n (%)
Clinical cure (score = 0)	32 (48.5)	12 (35.3)
Not clinical cure	32 (48.5)	19 (55.9)
Missing	2 (3.0)	3 (8.8)
Analysis method		
MI (average %) [1]	49.7	35.9
Difference (95% CI)		-6.6, 34.2
Missing as failures[2]	32 (48.5)	12 (35.3)
Difference (95% CI)		13.2 (-9.1, 35.5)

Source: Adapted from Table 14.2.3.13.3 and confirmed by reviewer using ADEFF dataset

[1] Missing values were imputed with multiple imputation method

[2] Missing values were counted as failures

Abbreviations: MI, multiple imputation; mITT, modified intent to treat.

The secondary endpoint results of time to first recurrence of a culture-verified acute VVC episode during the maintenance phase (post Day 14 through Week 50) are summarized in [Table 27](#) and presented in a Kaplan-Meier plot in [Figure 4](#). Actual known recurrence events occurred in 4 (2.7%) oteseconazole subjects and in 24 (33.3%) fluconazole/placebo subjects. Oteseconazole demonstrated superiority to fluconazole/placebo in the time to first recurrence of culture verified acute VVC infection based on the hazard ratio of 0.06 (p<0.001). Both treatment groups' median time to first recurrence of a culture-verified acute VVC episode were not reached because less than 50% of subjects had a recurrence event during the study. Note that subjects who did not enter the maintenance phase, including those who did not have successful treatment of their initial VVC episode or had no follow-up in the maintenance phase, were excluded from this analysis.

The recurrence events during the treatment post Day 14 through Week 12 included 2 (1.4%) subjects in the oteseconazole arm and 11 (15.3%) subjects in the fluconazole/placebo arm. After treatment completion through Week 50, 2 recurrence events (1.4%) occurred in the oteseconazole arm and 13 recurrence events (18.1%) occurred in the fluconazole/placebo arm. More recurrence events occurred in the fluconazole/placebo arm during the treatment and follow-up periods than in the oteseconazole arm.

Table 27. Time to First Recurrence of a Culture-Verified Acute VVC Episode For Trial CL-017 :ITT Population

Characteristic	Oteseconazole	Fluconazole /Placebo
	N=147 n (%)	N=72 n (%)
Known recurrence	4 (2.7)	24 (33.3)
Post Day 14 to Week12	2 (1.4)	11 (15.3)
Week 12 to end of study	2 (1.4)	13 (18.1)
Hazard ratio (95% CI)[1]	0.06 (0.02, 0.18)	
P-value[2]	<0.001	

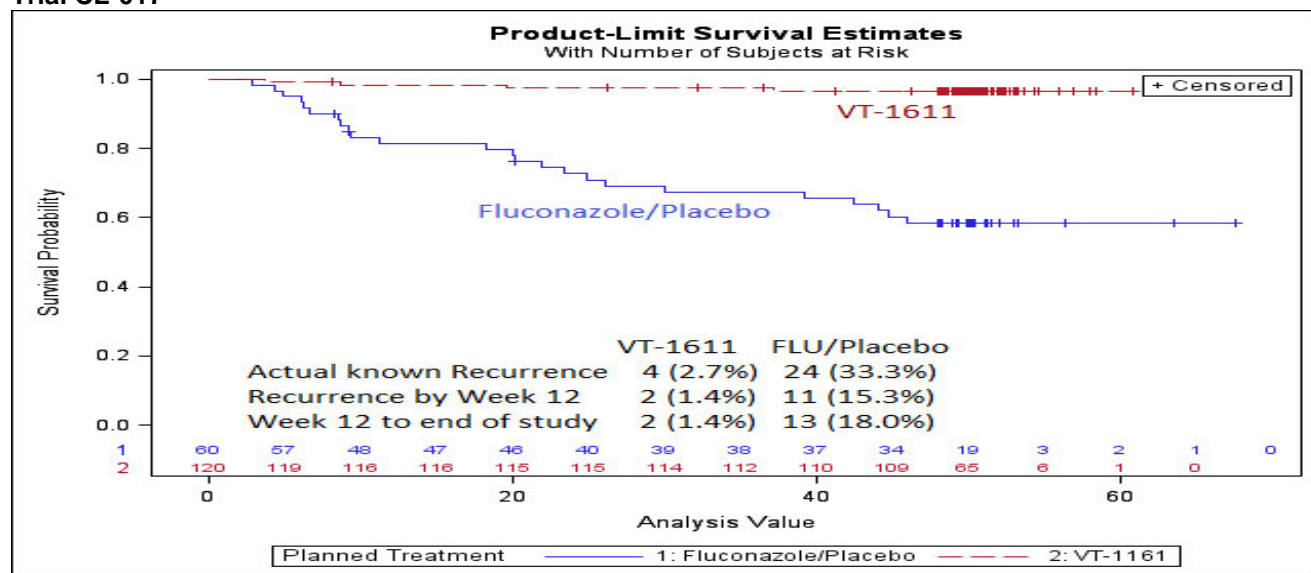
Source: Adapted from Table 14.2.3.1.1 and confirmed by reviewer using ADEFF dataset

[1]Based on analysis of subjects who entered the maintenance phase, i.e., 120 oteseconazole and 60 fluconazole/placebo subjects.

[2]: Log-rank test comparing active treatment to placebo:

Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

Figure 4. Kaplan-Meier Plot of Time to First Recurrence of Culture Verified Acute VVC Episode for Trial CL-017



Source: Reviewer conducted analysis using ADTTE dataset
 VT-1161=oteseconazole
 Abbreviations: Flu, fluconazole; VVC, vulvovaginal candidiasis.

Results of analyses of additional secondary endpoints are reported in Section 17.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Assessment of the Use of VVC Medication on the Interpretation of the Efficacy of Oteseconazole

Issue

Assessment of the use of VVC medication on the interpretation of the efficacy of oteseconazole.

Background

The definition of a recurrent episode of VVC required both a signs and symptoms score ≥ 3 as well as a positive culture for *Candida*. Per the protocols, investigators were allowed to offer VVC medication to a subject if they deemed there to be a clinical need when the subject had a signs and symptoms score ≥ 3 and a positive KOH. Whether or not someone was treated for a suspected VVC infection did not enter into the primary endpoint definition, but the use of other VVC medication during maintenance could confound the assessment of recurrence. Therefore, the use of VVC medication was explored and a sensitivity analysis in which subjects who received any other VVC medications were also treated as failures was considered to see if the use of VVC medication overly affected the results. Additionally, recurrence was alternatively defined based on a positive KOH rather than a positive culture as used in the primary endpoint definition. Recurrence defined in this manner may be more relevant from a patient perspective since a positive KOH was a trigger for treatment of VVC.

Assessment

[Table 28](#) summarizes the number of subjects who received VVC medication for a known recurrence, those who did not have a recurrence but who had incomplete follow-up, and those who had complete follow-up and no recurrence for Trials CL-011 and CL-012.

Table 28. Culture-Verified Acute VVC Recurrence and Receipt of VVC Medication During Maintenance (ITT Population), Trials CL-011 and CL-012

Response	CL-011		CL-012	
	Oteseconazole (N=217)	Placebo (N=109)	Oteseconazole (N=218)	Placebo (N=108)
Known recurrence n (%)	14 (6.5)	45 (41.3)	8 (3.7)	39 (36.1)
Received VVC med	12	44	8	38
No VVC med	2	1	0	1
No known recurrence but incomplete follow-up n (%)	37 (17.1)	8 (7.3)	33 (15.1)	12 (11.1)
Received VVC med	8	2	8	3
No VVC med	29	6	24	9
Unknown	0	0	1	0
No follow-up n (%)	5 (2.3)	3 (2.8)	5 (2.3)	1 (0.9)
No recurrence (complete follow-up) n (%)	161 (74.2)	53 (48.6)	172 (78.9)	56 (51.9)
Received VVC med	37	7	30	9
No VVC med	124	46	142	47

Source: Reviewer conducted analysis using ADEFF dataset
Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

Additional analyses of the primary endpoint that consider use of VVC medication as part of the definition of recurrence supported the significance of oteseconazole compared to placebo in the reduction of recurrence. For Trial CL-011, using multiple imputation to address subjects with incomplete data gave rates of recurrences of 27.3% on oteseconazole and 50.8% on placebo ($p < 0.001$). Alternatively, treating recurrences, VVC medication use, and incomplete follow-up as failures led to 93 (42.9%) events for oteseconazole compared to 63 (57.8%) for placebo ($p = 0.01$). For Trial CL-012, using multiple imputation to handle subjects with incomplete data gave rates of recurrences of 21.3% on oteseconazole and 49.7% on placebo ($p < 0.001$). Treating subjects who had missing data as having an event leads to 76 (34.9%) events on oteseconazole and 61 (56.5%) events on placebo ($p < 0.001$).

Recurrence based on the alternative definition of signs and symptoms score ≥ 3 and positive KOH is summarized in [Table 29](#) for Trials CL-011 and CL-012. Most of the use of VVC medication was captured using this definition of recurrence as few subjects without a recurrence received VVC medication. When treating incomplete follow-up as a failure, the rates of recurrence were 41.5% for oteseconazole compared to 55.0% for placebo ($p = 0.02$) in Trial CL-011 and 33.9% for oteseconazole compared to 52.8% for placebo ($p = 0.001$) in Trial CL-012.

Table 29. Recurrence Based on KOH Positive Acute VVC During Maintenance ITT Population Trials CL-011 and CL-012

Response	CL-011		CL-012	
	Oteseconazole (N=217)	Placebo (N=109)	Oteseconazole (N=218)	Placebo (N=108)
Known recurrence n (%)	54 (24.9)	49 (45.0)	37 (17.0)	43 (39.8)
Received VVC medication	53	48	37	43
No known recurrence but incomplete follow-up n (%)	36 (16.6)	11 (10.1)	37 (17.0)	14 (13.0)
Received VVC med	1	2	4	2
No recurrence (complete follow-up) n (%)	127 (58.5)	49 (45.0)	144 (66.1)	51 (47.2)
Received VVC medication	3	3	5	5

Source: Adapted from Tables A.14.2.1.5 in Submission 0054 dated 12/2/21
Abbreviations: ITT, intent-to-treat; KOH, potassium hydroxide; VVC, vulvovaginal candidiasis.

Additional important information to consider is the number of times a subject was treated with VVC treatments during the maintenance phase. Note that for a treatment to be considered a new treatment of VVC, by definition, it needed to have occurred 14 days after the previous one. The number of times a subject was treated with a VVC medication during the maintenance phase for Trials CL-011 and CL-012 is summarized in [Table 30](#).

For Trial CL-011, oteseconazole subjects had a mean number of VVC treatments of 0.54 while placebo subjects had a mean number of VVC treatments of 1.24. This difference is statistically significant. As shown in [Table 30](#), more placebo subjects than oteseconazole subjects were treated at least once with a VVC medication during the maintenance phase. For both treatment arms, most subjects received one or two treatments with a VVC medication although less for oteseconazole subjects compared to placebo subjects. However, 2 oteseconazole subjects were treated 9 and 11 times whereas the maximum number of times a placebo subject was treated was 8 times for 2 subjects.

For Trial CL-012, the mean number of VVC treatments on oteseconazole was significantly lower (0.35) than that on placebo (1.0). Similar to Trial CL-011, more placebo subjects than oteseconazole subjects were treated at least once with a VVC medication during the maintenance phase, and most received one or two treatments with a VVC medication, although less for oteseconazole subjects compared to placebo subjects. One oteseconazole subject was treated 8 times whereas 7 times was the maximum number of times a placebo subject was treated.

Table 30. Number of Times Treated With a VVC Medication During Maintenance (ITT Population), Trials CL-011 and CL-012

# of Times Treated With VVC Medication	CL-011		CL-012	
	Oteseconazole (N=217)	Placebo (N=109)	Oteseconazole (N=218)	Placebo (N=108)
0	160 (74%)	56 (51%)	169 (78%)	58 (54%)
1	30 (14%)	21 (19%)	32 (15%)	23 (21%)
2	14 (6%)	13 (12%)	9 (4%)	13 (12%)
3	6 (3%)	6 (6%)	2 (0.9%)	6 (6%)
4	3 (1%)	5 (5%)	0	3 (3%)
5	2 (0.9%)	3 (3%)	1 (0.5%)	2 (2%)
6	0	2 (2%)	0	2 (2%)
7	0	1 (0.9%)	1 (0.5%)	1 (0.9%)
8	0	2 (2%)	1 (0.5%)	0
9	1 (0.5%)	0	0	0
10	0	0	0	0
11	1 (0.5%)	0	0	0

Source: Tables 14.2.3.13.1 from the CL-011 and CL-012 study reports
Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

[Table 31](#) contains the number of subjects who received treatment with a VVC medication by those who had resolution of the initial VVC episode by Day 14, those who had known recurrence, those who did not have a recurrence but who had incomplete follow-up, and those who had complete follow-up for Trial CL-017. This trial was of a different design from CL-011 and -012 since subjects were followed from the start of the initial treatment and the initial treatment differed by arm (oteseconazole versus fluconazole). Thus, the format of [Table 31](#) differs from that of [Table 28](#).

Table 31. Resolution at Day 14 and Recurrence Based on Culture Verified Acute VVC and Receipt of VVC Medication During Maintenance ITT Population Trial CL-017

Response	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)
Resolved Day 14 and no recurrence (complete follow-up) n (%)	103 (70.1)	32 (44.4)
Received VVC med	43	11
No VVC med	60	21
Resolved Day 14 and no known recurrence but incomplete follow-up n (%)	26 (17.7)	9 (12.5)
Received VVC med	6	0
No VVC med	20	9
Resolved Day 14 AND recurrence n (%)	4 (2.7)	24 (33.3)
Received VVC med	3	19
No VVC med	1	5
Not resolved Day 14 n (%)	10 (6.8)	3 (4.2)
No follow-up n (%)*	4 (2.7)	4 (5.6)

Source: Reviewer conducted analysis using ADEFF dataset

*All missing VVC treatment during maintenance info, since subject who were not resolved by Day 14 were not followed in maintenance phase

Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

As with the other studies, additional analyses of the primary endpoint that consider use of VVC medication as part of the definition of recurrence supported the significance of oteseconazole compared to fluconazole/placebo in the reduction of recurrence. Using multiple imputation to address subjects with incomplete data gave rates of recurrences of 43.5% on oteseconazole and 59.0% on fluconazole/placebo (p=0.039). Alternatively, treating recurrences, VVC medication,

and incomplete follow-up as failures led to 87 (59.2%) events for oteseconazole compared to 51 (70.8%) for fluconazole/placebo.

Failure to resolve at Day 14 or recurrence during the maintenance phase based on the alternative definition of signs and symptoms score ≥ 3 and positive KOH is summarized in [Table 32](#) for Trial CL-017. Similar to what was seen in the other studies, most of the use of VVC medication during the maintenance phase was captured in this definition of recurrence as few subjects without a recurrence received VVC medication. When treating incomplete follow-up as a failure, the rates of failure to resolve at Day 14 or recurrence during the maintenance phase were 51.0% for oteseconazole compared to 66.7% for fluconazole/placebo (p=0.028).

Table 32. Failure to Resolve at Day 14 or Recurrence Based on KOH Positive Acute VVC During Maintenance ITT Population Trials CL-017

Characteristic	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)
Failed to resolve Day 14 or known recurrence	50 (34.0)	32 (44.4)
Failed to Resolve	10 (6.8)	3 (4.2)
Known Recurrence	40 (27.2)	29 (40.3)
Received VVC medication	39	29
No known recurrence but incomplete follow-up	25 (17.0)	16 (22.2)
Received VVC medication	1	0
No recurrence (complete follow-up)	72 (49.0)	24 (33.3)
Received VVC medication	9	1

Source: Adapted from Tables A.14.2.1.5 in Submission 0054 dated 12/2/21
Abbreviations: ITT, intent-to-treat; KOH, potassium hydroxide; VVC, vulvovaginal candidiasis

The number of times a subject was treated with a VVC treatment during the maintenance phase (post Day 14 through Week 50) for Trial CL-017 is summarized in the following table. Note that subjects who did not resolve by Day 14 or who had no follow-up were not included.

Oteseconazole subjects had a mean number of VVC treatments of 0.74 while fluconazole/placebo subjects had a mean number of VVC treatments of 1.26. Although overall, fewer oteseconazole subjects did not receive treatment with a VVC medication during the maintenance phase, a slightly higher percentage of oteseconazole subjects compared to placebo subjects received a single treatment with a VVC medication.

Table 33. Number of Times Treated With a VVC Medication During Maintenance Phase ITT Population Trial CL-017

# of Times Treated With VVC Medication	Oteseconazole (N=147) n (%)	Placebo (N=72) n (%)
0	82 (56%)	35 (49%)
1	31 (21%)	14 (19%)
2	9 (6%)	4 (6%)
3	5 (3%)	4 (6%)
4	1 (0.8%)	3 (4%)
5	1 (0.8%)	1 (1%)
6	3 (2%)	1 (1%)
7	1 (0.8%)	2 (3%)
8	0	0
9	0	0
10	0	0
11	0	1 (1%)

Source Table 14.2.3.12.1 from CL-017 study report
Abbreviations: ITT, intent-to-treat; VVC, vulvovaginal candidiasis.

Conclusion

Although there was a large number of subjects who received additional VVC medication in both arms within each study, the difference between treatments, though smaller than that observed for the primary endpoint, was still significantly different in favor of the oteseconazole arm when the use of VVC medication was included in the definition of recurrence or when the definition of recurrence was based on a positive KOH rather than a positive culture. From a patient perspective, the need for additional VVC treatment due to the presence of signs and symptoms may be more important than having a culture-verified episode of VVC when determining the effect of maintenance treatment. Therefore, it is recommended that, in addition to the protocol-specified primary endpoint, the results of the analyses that include the use of VVC medication in the definition of recurrence or the alternate definition of recurrence also be included in Section 14: Clinical Studies of the product labelling.

6.3.2

(b) (4)

Issue

(b) (4)

Background

(b) (4)

Assessment

(b) (4)

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(b) (4)

Conclusion

(b) (4)

(b) (4) Therefore, a statistical assessment of (b) (4)
(b) (4)
(b) (4) could not be made.

6.3.3. Support for Proposed Indications

Issue

The Applicant's proposed indication statement is: (b) (4)
(b) (4)

Background

(b) (4)

Assessment

The focus of the development program for oteseconazole was (b) (4)
(b) (4)
(b) (4) it is now the Division's opinion

that the more appropriate wording of this indication should be to reduce the incidence of recurrent VVC

(b) (4)
(b) (4)

(b) (4)

Conclusion

The clinical program supports only an indication for reducing the incidence of RVVC.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical data submitted to support the safety evaluation of oteseconazole included pharmacology (primary, secondary and safety pharmacology), pharmacokinetics (absorption, distribution, metabolism, excretion with toxicokinetics for pivotal studies) and toxicology (repeat-dose, genotoxicity, carcinogenicity, reproductive toxicity) studies in rats (up to two years), dogs (up to 39 weeks), mice (up to 26 weeks) and rabbits (during pregnancy to evaluate embryo-fetal toxicity). The identified risks should be manageable in the indicated population.

Pharmacology and Pharmacokinetics

In vitro studies showed that oteseconazole inhibited sterol 14-demethylation in two strains of *Candida albicans* and almost completely blocked formation of ergosterol, leading to the

accumulation of lanosterol and other toxic methylated steroids. In vitro binding studies showed oteseconazole inhibited binding most potently at the rat cerebral cortex Cl⁻ channel, the human adenosine A₃ receptor, and the human melatonin MT₁ receptors. Oteseconazole was also shown to inhibit the human efflux transporter breast cancer resistance protein with a half maximal inhibitory concentration (IC₅₀) of 0.4 μM. Oteseconazole administered as a single oral dose (up to 1000 mg/kg) had no significant effect on neurobehavioral or respiratory function in rats. Similarly, a single oral dose (up to 300 mg/kg) had no significant effect on cardiovascular function in dogs. In rats and dogs, oteseconazole exposure was less dose proportional and the drug accumulated up to 126-fold in dogs with repeated dosing over 39 weeks. The half-life was 30 days in dogs and 8.5 days in rats. In a tissue distribution study in rats, the highest levels of oteseconazole were observed in the small intestines and in the Harderian gland.

Toxicology

Reproductive and developmental toxicology studies included fertility studies in male and female rats, embryo-fetal development studies in rats and rabbits, and four pre- and postnatal development studies in rats. Although fertility was unaffected, increased incidences of abnormal sperm were observed at 3 mg/kg/day and sperm counts were reduced at 10 mg/kg/day. Fertility in female rats was comparable to that of controls after exposure to oteseconazole. There was no embryo-fetal toxicity or malformations at 40 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rats. Abortions occurred in rabbits in the presence of maternal toxicity (reduced bodyweight gain with reduced food consumption), but there were no drug-related malformations at 15 mg/kg/day following administration of oteseconazole during organogenesis in pregnant rabbits. In pre- and postnatal studies, oteseconazole administration to pregnant and lactating rats at 7.5 mg/kg/day resulted in lens opacities, swollen eyes, hemorrhage, hyphema, buphthalmos, corneal ulceration, retinal and optic nerve atrophy, as well as lens degeneration. Opacities were consistently found regardless of the strain of rat tested.

Oteseconazole was negative in the bacterial reverse mutation assay, in vitro chromosomal aberration assay, and in vivo micronucleus assay in rats.

In a 2-year oral carcinogenicity study of oteseconazole, male Sprague Dawley rats showed increased incidence of Leydig cell adenomas of the testes and thyroid follicular cell adenomas/carcinomas combined at ≥1.5 mg/kg/day. In females, thyroid follicular cell adenomas and carcinomas were increased at ≥1.5 mg/kg/day and thyroid carcinomas were increased at 5/3 mg/kg/day. Hemorrhage was increased in several tissues in male rats, but fewer tissues were affected in female rats (details below).

There was no increase in the incidence of tumors following daily oral administration of oteseconazole to Tg.rasH2 mice for 6 months at doses of 5 mg/kg/day in males and 15 mg/kg/day in females.

There are no safety concerns regarding the observed or potential impurities in oteseconazole. The limit for each individual related product was set at ≤0.2%, consistent with International Conference on Harmonisation (ICH) Q3B(R2) and was within applicable ICH M7(R1) limits based upon a maximum daily dose of 600 mg (June 2006; March 2017). All individual impurities have been detected at less than (b) (4) %. No (b) (4) were detected in the oteseconazole drug substance manufacturing process. The risk for (b) (4) formation appears to be very low.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Oteseconazole is an azole antifungal. Well-known azole associated adverse reactions include hepatic injury/hepatotoxicity, arrhythmias and QT-prolongations, embryo-fetal toxicity, and hypersensitivity reactions. Adverse reactions that are not azole class specific but have been identified in at least one drug in this class include visual disturbances; photosensitivity; severe cutaneous reactions (e.g., Stevens-Johnson syndrome [SJS], toxic epidermal necrolysis [TEN], and drug reaction with eosinophilia and systemic symptoms [DRESS]); adrenal dysfunction (e.g., Cushing syndrome or adrenal insufficiency); fluorosis; and electrolyte imbalances. Azole class-associated treatment-emergent adverse events (TEAEs) identified during review of oteseconazole are discussed in greater detail under Section [17.3](#) of this review.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

There is no available postmarket experience with oteseconazole at this time.

7.4. FDA Approach to the Safety Review

Three phase 3 trials, Trials CL-011, CL-012, and CL-017, were most relevant to the safety review of oteseconazole. The phase 2b dose-finding study, Trial CL-006, provided additional support for oteseconazole safety. While not a focal point of the safety evaluation, oteseconazole safety was further characterized by review of TEAEs reported in the Applicant's phase 1 PK studies and non-RVVC phase 2a studies. These studies are also briefly discussed in this review.

Using MAED, the clinical reviewer generated SMQ listings of well-documented adverse reactions associated with commonly used azole antifungals (e.g., fluconazole, voriconazole, posaconazole) including: hepatotoxicity, QT-prolongation and arrhythmia, phototoxicity/skin reactions, visual disturbances, and pancreatitis. Since hypersensitivity is a contraindication for any drug, CMQs/SMQs associated with hypersensitivity reactions were generated using Medical Dictionary for Regulatory Activities versions 21.0 (for Trials CL-011, -012, and -017) and 17.1 (for Trial CL-006).

7.5. Adequacy of Clinical Safety Database

A total of 1,663 subjects were included in the 13 phase 1 to 3 trials the Applicant conducted in support of the clinical development of oteseconazole. Of these subjects, 1,655 comprised the Applicant's clinical safety development program. Eight subjects, all in the phase 2/3 trials, were enrolled but not dosed and were, therefore, not included in the overall safety population for any of several reasons (e.g., investigator discretion, withdrawal of consent, being lost to follow-up or a screen failure, etc.).

The Applicant's clinical safety development program included 1,655 subjects who comprised the entire safety population, 1,221 of whom received at least one dose of oteseconazole and 434 of whom received at least one dose of placebo. The 1,221 subjects in the oteseconazole arm were enrolled in at least one of 13 clinical trials supportive of oteseconazole's development: four

phase 1 single-dose trials in healthy volunteers (Trials CL-001, CL-007 [PKE cohort], CL-013, and CL-016); two phase 1 multiple-dose trials in healthy volunteers (Trials CL-002 and CL-008); two phase 2 trials comprised of non-RVVC subjects (Trials CL-003 and CL-005); a single phase 2a acute VVC trial (Trial CL-004); a single phase 2 dose-finding trial (Trial CL-006), and three phase 3 trials (Trials CL-011, CL-012, and CL-017). Of the 1,082 subjects enrolled and randomized into the phase 2/3 RVVC studies, 746 subjects were assigned to receive oteseconazole and 336 subjects were assigned to receive placebo. A total of 621 subjects, all of whom were in the phase 3 trials and 41 of whom were in the phase 2 dose-ranging trial (CL-006), received the to-be-marketed oteseconazole dosing of a 1,050 mg loading dose (LD) and a 1,650 mg maintenance dose (MD).

As stated above, the primary focus of this review was assessing oteseconazole safety in the three phase 3 trials (Trials CL-011, CL-012, and CL-017), with a secondary focus on the phase 2 dose-finding trial (Trial CL-006) conducted in support of oteseconazole safety. The clinical reviewer considered the overall size of the oteseconazole safety database adequate.

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Table 35. Duration of Exposure, Safety Population, Trials 011, 012, 017 and 006 (ISS)

Variable	OTE Trial 011 N=217	PLB Trial 011 N=110	OTE Trial 012 N=217	PLB Trial 012 N=109	OTE Trial 017 N=146	PLB Trial 017 N=72	Pooled OTE Phase 3 N=580	Pooled PLB Phase 3 N=291	OTE Trial 006 N=166	PLB Trial 006 N=45
Duration of exposure, weeks										
Mean (SD)	11.3 (2.6)	11.4 (2.4)	11.4 (2.5)	11.1 (3)	10.1 (4.2)	9.8 (4.3)	11 (3.1)	10.9 (3.2)	16.8 (7.2)	21.7 (5.9)
Median (Q1, Q3)	12.1 (11.9, 12.3)	12.1 (12, 12.1)	12.1 (12, 12.1)	12.1 (12, 12.2)	12 (11.7, 12.1)	12 (10.9, 12.1)	12.1 (11.9, 12.1)	12.1 (12, 12.1)	14.7 (12.1, 24)	24 (23.1, 24)
Min, max	0.4, 16.9	1, 13	1, 13.3	0.1, 13.3	0.1, 13.3	0.1, 13.1	0.1, 16.9	0.1, 13.3	0.1, 26	1, 25
Total exposure (person years)	47	24	47	23	28	14	123	61	53	19
Patients treated, by duration, n (%)										
<12 weeks	55 (25.3)	25 (22.9)	43 (19.8)	20 (18.2)	52 (35.6)	24 (33.3)	150 (25.9)	69 (23.7)	22 (13.3)	5 (11.1)
≥12 to <26 weeks	162 (74.7)	84 (77.1)	174 (80.2)	90 (81.8)	94 (64.4)	48 (66.7)	430 (74.1)	222 (76.3)	142 (85.5)	40 (88.9)
≥26 to <50 weeks	0	0	0	0	0	0	0	0	2 (1.2)	0
≥50 to <100 weeks	0	0	0	0	0	0	0	0	0	0
≥100 weeks	0	0	0	0	0	0	0	0	0	0

Source: adsl.xpt; Software: R

Abbreviations: ISS, integrated summary of safety; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OTE, oteseconazole; PLB, placebo; Q1, first quartile; Q3, third quartile; SD, standard deviation

Mean and median durations of drug exposure, in weeks, in all phase 3 trials were mostly balanced across oteseconazole and placebo treatment arms, with most subjects remaining on the study arm over a median of 12 weeks in the pooled phase 3 analysis. A 12-week duration of exposure is consistent with the written protocols.

Similarly, the percentage of patients remaining in Trials CL-011 and CL-012 was balanced across treatment arms, with approximately three-quarters or more of all subjects exposed to the study drug for ≥ 12 to < 26 weeks. In Trial CL-017, while the duration of treatment across both the oteseconazole and placebo arms was balanced, with 64.4% and 66.7% of subjects receiving ≥ 12 to < 26 weeks of treatment, respectively, the percentage of subjects in this trial was slightly less than the percentages in Trials CL-011 and CL-012.

There was a noticeable difference between the oteseconazole and placebo arms in the phase 2b Trial CL-006, with the mean and median durations of exposure of 16.8 and 14.7 weeks, respectively, in the oteseconazole arm being considerably less than the mean and median durations of exposure in the placebo arm, 21.7 and 24, respectively. This discrepancy is likely because placebo subjects received treatment for 24 weeks, while oteseconazole subjects received 12 or 24 weeks of treatment. The majority of patients in this trial remained in the study from between ≥ 12 to < 26 weeks, 85.5% and 88.9%, respectively.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Overall Adverse Event Summaries

Phase 3 Trials CL-011, CL-012, and CL-017

A tabular overview of all TEAEs occurring in the phase 3 trials is shown in [Table 36](#) below. A total of 871 participants comprised the pooled phase 3 safety population: 580 in the oteseconazole arm and 291 in the placebo arm.

The percentages of all TEAEs across the oteseconazole and the placebo arms were nearly equal, with the exception being Trial CL-017, in which a larger percentage of TEAEs occurred in the placebo arm than in the oteseconazole arm (63.9% in placebo versus 54.1% in oteseconazole). There were few SAEs in the three phase 3 trials, and the number of SAEs across both treatment arms were near balanced. A single death occurred among the 871 subjects of the pooled phase 3 safety population, Subject (b) (4), (b) (6), (b) (3) in the oteseconazole arm of Trial CL-017. This participant is discussed in greater detail below; however, the death was deemed to be unrelated to oteseconazole exposure.

In the pooled phase 3 analysis, slightly more severe TEAEs occurred in subjects in the oteseconazole arm, whereas moderate and mild TEAEs were similar across the study arms. Few subjects experienced nonfatal moderate to severe TEAEs. This was most likely due to the disease entity being studied (RVVC) and the younger study population consisting of primarily young females (most of whom were between 18 to 34 years of age) who were generally healthy and with few co-morbid conditions.

Similarly, few TEAEs leading to study discontinuation occurred in the pooled phase 3 safety population, with near equal percentages of subjects discontinuing study treatment across

NDA 215888
Vivjoa (oteseconazole)

treatment arms (0.7% versus 0.3%, respectively, in the pooled oteseconazole and placebo arms), and with slightly more discontinuations occurring among oteseconazole subjects (four subjects versus one subject).

Irrespective of treatment arm, most TEAEs occurred in the Infections and infestations, Gastrointestinal disorders, Reproductive systems and breast disorders, and Nervous system SOCs. The reader is referred to Section [7.6.5](#) for more details.

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Table 36. Overview of Treatment-Emergent Adverse Events, Safety Population, Trials 011, 012, and 017 (ISS)

Event Category	OTE Trial 011 N=217 n (%)	PLB Trial 011 N=110 n (%)	OTE Trial 012 N=217 n (%)	PLB Trial 012 N=109 n (%)	OTE Trial 017 N=146 n (%)	PLB Trial 017 N=72 n (%)	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)	Risk Difference Pooled Phase 3 (%) (95% CI)
Any treatment-emergent AE	129 (59.4)	63 (57.8)	112 (51.6)	63 (57.3)	79 (54.1)	46 (63.9)	320 (55.2)	172 (59.1)	-3.9 (-10.9, 3.0)
Moderate or severe AEs (Grade 3-5)	7 (3.3)	2 (1.8)	10 (4.6)	3 (2.7)	5 (3.5)	3 (4.2)	22 (3.8)	8 (2.7)	1.1 (-3.6, 2.9)
SAEs	3 (1.4)	3 (2.8)	7 (3.2)	5 (4.5)	3 (2.1)	1 (1.4)	13 (2.2)	9 (3.1)	-0.9 (-3.2, 1.5)
SAEs with fatal outcome	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Nonfatal SAEs	3 (1.4)	3 (2.8)	7 (3.2)	5 (4.5)	2 (1.4)	1 (1.4)	12 (2.1)	9 (3.1)	-1.0 (-3.3, 1.3)
Life-threatening SAEs*	1 (0.5)	0	0	0	1 (0.7)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
AE leading to discontinuation of study drug	1 (0.5)	0	2 (0.9)	1 (0.9)	1 (0.7)	0	4 (0.7)	1 (0.3)	0.3 (-0.6, 1.3)
AE leading to dose modification of study drug	1 (0.5)	1 (0.9)	0	2 (1.8)	0	0	1 (0.2)	3 (1.0)	-0.9 (-2.1, 0.4)
AE leading to interruption of study drug	1 (0.5)	1 (0.9)	0	2 (1.8)	0	0	1 (0.2)	3 (1.0)	-0.9 (-2.1, 0.4)
AE leading to reduction of study drug	0	0	0	0	0	0	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0	0	0	0	0	0	0 (0, 0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment emergent.

Duration is approx. 50 weeks.

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

*There are two subjects who experienced life-threatening but nonfatal SAEs: VMT-VT-1161-CL-011 (b) (6) (age: 51; race: Black or African American; preferred term: Limb traumatic amputation); VMT-VT-1161-CL-017 (b) (6) (age: 38; race: White; preferred terms: cerebrovascular accident; retroperitoneal hemorrhage; deep vein thrombosis; pulmonary embolism).

Abbreviations: AE, adverse event; CI, confidence interval; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with at least one event; OTE, oteseconazole; PLB, placebo; SAE, serious adverse event

Baseline Demographic Characteristics

The phase 3 safety population was similar to the ITT population. The majority of females in both the oteseconazole and placebo arms were White (75.0% oteseconazole versus 75.3% placebo), non-Latino females (84.8% versus 85.2%) with an overall mean age and mean baseline BMI of 34.5 and 26, respectively. The majority of females were either on hormonal contraceptives or had an inserted intrauterine device. Most females were from the United States (53.6% versus 51.9%), followed by females from European countries (39.5% versus 41.2%), most of whom were from Eastern Europe. Please refer to [Table 169](#) in the Appendix for further details.

Past Medical History

Among the 871 subjects in the combined phase 3 trials, a total 653 (75.0%) subjects (429 oteseconazole subjects and 224 placebo subjects) were reported to have had prior medical conditions.

The most common medical conditions among oteseconazole subjects included: anxiety/anxiety disorders and symptoms (PT: anxiety, anxiety disorder, generalized anxiety disorder) (78 subjects); seasonal allergy (72 subjects); caesarean section (65 subjects); headaches/migraines (PT: headache, migraine, migraine without aura, retinal migraine, tension headache) (64 subjects); depression/depressed mood disorders and disturbances (PT: depression, major depression, perinatal depression, persistent depressive disorder) (56 subjects); hypertension (52 subjects); drug hypersensitivity/allergic conditions (PT: drug hypersensitivity, hypersensitivity, rubber sensitivity) (48 subjects); asthma (37 subjects); gastroesophageal reflux disease (35 subjects); hysterectomy (35 subjects); female sterilization (32 subjects); hypothyroidism (32 subjects).

Among placebo subjects, the most common prior medical conditions included: headaches (PT: headache, migraine, migraine with aura, migraine without aura, post-traumatic headache, sinus headache, tension headache) (35 subjects); caesarean section (31 subjects); seasonal allergy (31 subjects); anxiety/anxiety disorders and symptoms (PT: anxiety, anxiety disorder) (27 subjects); depression/depressed mood disorders and disturbances (PT: depression, depressed mood) (26 subjects); hypertension (PT: hypertension, essential hypertension) (25 subjects); drug hypersensitivity/allergic conditions (PT: drug hypersensitivity, hypersensitivity, multiple allergies, rubber sensitivity) (24 subjects); female sterilization (20 subjects); hysterectomy (20 subjects); gastroesophageal reflux disease (19 subjects).

Phase 2 Trial CL-006

The phase 2b safety population was comprised of 211 subjects: 166 subjects in the combined oteseconazole arms and 45 subjects in the placebo arm. The 166 oteseconazole subjects were subdivided into 4 treatment arms which included: 41 subjects in the 150 mg x 12 weeks arm; 42 subjects in the 150 mg x 24 weeks arm; 42 subjects in the 300 mg x 12 weeks arm; and 41 subjects in the 150 mg x 24 weeks arm.

A summary of all Trial CL-006 TEAEs is provided below. There were a total of 447 TEAEs nearly evenly distributed across all five treatment arms of Trial CL-006, with noticeably fewer numbers of TEAEs in the 300 mg x 24 weeks (n=77 TEAEs) dose arm. Otherwise, there were 95, 88, and 95 TEAEs occurring in the oteseconazole 150 mg x 12 weeks, 150 mg x 24 weeks, 300 mg x 12 weeks arms, respectively, and 92 TEAEs in the placebo.

NDA 215888
Vivjoa (oteseconazole)

No fatal serious adverse events (SAEs) occurred among any subjects in Trial CL-006. There was a total of five nonfatal SAEs in the combined oteseconazole arm, two of which occurred in the same subject (Subject (b) (6)—PTs: abdominal pain and acute pancreatitis) compared with one subject who experienced a single nonfatal SAE in the placebo arm (PT: appendicitis). There were only two subjects, both from the oteseconazole arm, who prematurely discontinued the study drug, with one of these TEAEs being an SAE (Subject (b) (6) PT: dermatitis allergic; and Subject (b) (6) PT: Pancreatitis [SAE]). Most TEAEs were either mild or moderate and occurred in near similar percentages across all treatment arms. However, the fewest number of mild TEAEs occurred in the oteseconazole 300 mg x 24 weeks arm, and the highest number of severe TEAEs occurred in this treatment arm as well.

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Table 37. Overview of Treatment-Emergent Adverse Events, Safety Population, Trials 006 (ISS)

Event Category	150 mg 12 week (N=41)		150 mg 24-week (N=42)		300 mg 12 week (N=42)		300 mg 24-week (N=41)		Total Oteseconazole (N=166)		Placebo (N=46)	
	Subjects n(%)	No. Events	Subjects n(%)	No. Events	Subjects n(%)	No. Events	Subjects n(%)	No. Events	Subjects n(%)	No. Events	Subjects n(%)	No. Events
No. of subjects with SAEs	1 (2.4)	2	0 (0.0)	0	1 (2.4)	1	2 (4.9)	2	4 (2.4)	5	1 (2.2)	1
Fatal	0	0	0	0	0	0	0	0	0	0	0	0
Nonfatal SAEs	1	2	0	0	1	1	2	2	4 (2.4)	5	1	1
Life-threatening SAEs	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to discontinuation of study drugs	1 (2.4)	1	0 (0.0)	0	1 (2.4)	1	0 (0.0)	0	2 (1.2)	2	0	0
AE leading to interruption of study drugs*	2 (4.9)	6	0	0	0	0	0	0	2 (1.2)	6	0	0
No. subjects with at least 1 TEAE	26 (63.4)	95	31 (73.8)	88	30 (71.4)	95	28 (68.3)	77	115	355	35 (77.8)	92
Mild	11 (26.8)	65	12 (28.6)	48	12 (28.6)	56	14 (34.1)	39	49 (29.5)	208	16 (35.6)	57
Moderate	15 (36.6)	28	18 (42.9)	39	15 (35.7)	36	12 (29.3)	28	60 (36.1)	131	18 (40.0)	34
Severe	1 (2.4)	2	1 (2.4)	1	3 (7.1)	3	2 (4.9)	10	7 (4.2)	16	1 (2.2)	1

Source: ADAE data sets created by clinical reviewer with reference to Trial CL-006 clinical study report.

Note: *Several subjects had more than 1 TEAE.

Abbreviations: AE, adverse event; ISS, integrated summary of safety; SAE, severe adverse event; TEAE, treatment-emergent adverse event.

Baseline Demographic Characteristics and Past Medical History

The safety population of Trial CL-006 was comprised mostly of White, non-Latino females with an overall mean age and mean baseline BMI of 34.8 and 27.4, respectively. The most common medical conditions found among participants randomized to oteseconazole included bacterial vaginosis, depression, obesity, and anxiety, whereas in the placebo arm, bacterial vaginosis was the most common medical condition. A summary of baseline demographic features of subjects in Trial CL-006 is found in Section [16.5](#) in the Appendix.

7.6.2. Deaths

Phase 3 Trials CL-011, CL-012, and CL-017

A single treatment-emergent death (Subject (b) (6)) occurred in the pooled phase 3 trials. Subject (b) (6) was a 50-year-old female who upon enrolling into Trial CL-017 was randomized to receive oteseconazole treatment. The subject's death from COVID-19-associated acute respiratory failure is described in detail below, and was assessed by the Applicant, the Study Investigator and the clinical reviewer as being unrelated to oteseconazole. In addition, this was the single reported death to occur in any treatment arm among the major phase 2-3 trials conducted in support of oteseconazole's clinical development, which is largely reflective of the disease entity, RVVC, and the target population which was primarily generally healthy young females.

Subject (b) (6) (Oteseconazole)

(Fatal SAE PT: Acute respiratory failure/Nonfatal SAE PT: Pneumonia viral)

A 50-year-old White, non-Latino American female with a prior medical history most noted for Sjögren's syndrome (since (b) (6)), treated with hydroxychloroquine (Plaquenil) and cevimeline HCl (Evoxac; for treatment of symptoms of dry mouth in patients with Sjögren's syndrome); hypertension (since (b) (6)); obesity (BMI 31.3); depression (since (b) (6)); and a history of RVVC, with three prior episodes of acute VVC within the 12 months prior to study enrollment.

On Study Day 279, the subject was diagnosed with COVID-19 pneumonia (nonfatal PT: pneumonia viral), for which the subject was hospitalized. According to the Applicant, limited details on hospitalization were available. Action taken with study drug was listed as "new drug therapy added and discontinued from study." The subject was reported to have developed a fatal SAE on Study Day 305 (PT: acute respiratory failure) due to COVID-19. Subject's date of death and final day in the study were the same, Study Day 305.

Study Investigator's/Applicant's Impression: The study investigator and the Applicant assessed the event (PTs: pneumonia viral [COVID-19] and acute respiratory failure) as being unrelated to oteseconazole exposure.

Clinical Reviewer's Assessment: *On review of the accompanying case narrative and clinical data, the reviewer agrees with the Study Investigator and Applicant that the fatal SAE (PT: acute respiratory failure) was unrelated to oteseconazole but was instead due to infection with COVID-19 in a person who was immunocompromised with a rheumatologic condition, Sjogren's syndrome, and with a BMI of 31.3.*

Phase 2b Trial CL-006

No fatal events occurred in Trial CL-006.

7.6.3. Nonfatal Serious Adverse Events

Phase 3 Trials CL-011, CL-012, and CL-017

A total of 35 nonfatal treatment-emergent SAEs occurred in 22 (22/871; 2.5%) subjects during the phase 3 trials: 12 events in CL-011, 15 events in CL-012, and 8 events in CL-017. Eighteen nonfatal SAEs occurred in 13 subjects (13/580; 2.2%) randomized to the oteseconazole arms, (including Subject (b) (6) [in CL-011] and Subject (b) (6) [in CL-017] with 2 and 5 nonfatal SAEs, respectively), and 17 nonfatal SAE events occurred in 9 subjects (9/291; 3.1%) receiving placebo, including two subjects each with more than one nonfatal SAE (Subject (b) (6) with six nonfatal SAEs in CL-011 and Subject (b) (6) in CL-012 with four separate nonfatal SAEs all coded to PT depression).

All nonfatal SAEs in the oteseconazole arm were deemed either unrelated to or unlikely to be related to the study drug by the Applicant and Study Investigators. All but two resulted in the resolution of the recorded events, and none required a change in oteseconazole dosing. Four nonfatal SAEs in the oteseconazole arm occurred while on study drug, and the other 14 events occurred while subjects remained enrolled in the study but were no longer receiving study drug. The clinical reviewer conducted a detailed review of all phase 3 nonfatal SAEs and agrees with the Applicant and Study Investigators that no nonfatal SAEs occurring in the oteseconazole arm were attributable to oteseconazole exposure.

Most nonfatal SAEs occurring in the placebo arm occurred under the Infections and infestations system organ class (SOC), in a total of five subjects with six documented nonfatal SAEs. Three nonfatal SAEs in the placebo arm occurred while the subjects were on treatment, while all other treatment-emergent nonfatal SAEs occurred while the subjects remained in the study but were no longer receiving treatment. All nonfatal SAEs in the placebo arm were considered unrelated to study treatment by the Study Investigator and Applicant; all but one recovered from the event and no subjects required a change in study drug dosing (with data missing for one patient).

Refer to Section [17.1](#) in the Appendix for narratives of all the pooled phase 3 nonfatal SAEs.

Table 38. Serious Adverse Events by System Organ Class and Preferred Term, Pooled Phase 3 Safety Population, Trials CL-011, -012, and -017 (ISS)

System Organ Class Preferred Term	OTE Trial 011 N=217 n (%)	PLB Trial 011 N=110 n (%)	OTE Trial 012 N=217 n (%)	PLB Trial 012 N=109 n (%)	OTE Trial 017 N=146 n (%)	PLB Trial 017 N=72 n (%)	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)	Risk Difference Pooled Phase 3 (%) (95% CI)
Blood and lymphatic system disorders	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Anemia	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Cardiac disorders	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Myocarditis	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Gastrointestinal disorders	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Retroperitoneal hemorrhage	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Abdominal pain	0	0	0	0	0	0	0	0	0 (0, 0)
Pancreatitis	0	0	0	0	0	0	0	0	0 (0, 0)
Infections and infestations	2 (0.9)	2 (1.8)	2 (0.9)	2 (1.8)	2 (1.4)	1 (1.4)	6 (1.0)	5 (1.7)	-0.7 (-2.4, 1.0)
Appendicitis	0	1 (0.9)	0	0	1 (0.7)	0	1 (0.2)	1 (0.3)	-0.2 (-0.9, 0.6)
Pneumonia viral	0	0	0	1 (0.9)	1 (0.7)	0	1 (0.2)	1 (0.3)	-0.2 (-0.9, 0.6)
Bronchitis	0	1 (0.9)	0	0	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Cholecystitis infective	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Meningitis viral	0	0	0	0	0	0	0	0	0 (0, 0)
Paronychia	0	0	0	0	0	0	0	0	0 (0, 0)
Pneumonia	0	1 (0.9)	0	0	0	1 (1.4)	0	2 (0.7)	-0.7 (-1.6, 0.3)
Postoperative wound infection	1 (0.5)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Severe acute respiratory syndrome	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Sinusitis	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Tubo-ovarian abscess	1 (0.5)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Injury, poisoning and procedural complications	1 (0.5)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Limb traumatic amputation	1 (0.5)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Musculoskeletal and connective tissue disorders	0	0	2 (0.9)	0	0	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Arthralgia	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Back pain	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Breast cancer female	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Nervous system disorders	0	0	1 (0.5)	0	1 (0.7)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Cerebrovascular accident	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)

System Organ Class Preferred Term	OTE Trial 011 N=217 n (%)	PLB Trial 011 N=110 n (%)	OTE Trial 012 N=217 n (%)	PLB Trial 012 N=109 n (%)	OTE Trial 017 N=146 n (%)	PLB Trial 017 N=72 n (%)	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)	Risk Difference Pooled Phase 3 (%) (95% CI)
Motor dysfunction	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Psychiatric disorders	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Depression	0	0	0	1 (0.9)	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Reproductive system and breast disorders	1 (0.5)	1 (0.9)	1 (0.5)	0	0	0	2 (0.3)	1 (0.3)	0.0 (-0.8, 0.8)
Endometriosis	1 (0.5)	0	0	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Uterine polyp	0	0	1 (0.5)	0	0	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Vaginal hemorrhage	0	1 (0.9)	0	0	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Respiratory, thoracic and mediastinal disorders	0	1 (0.9)	0	0	2 (1.4)	0	2 (0.3)	1 (0.3)	0.0 (-0.8, 0.8)
Acute respiratory failure	0	1 (0.9)	0	0	1 (0.7)	0	1 (0.2)	1 (0.3)	-0.2 (-0.9, 0.6)
Pulmonary embolism	0	0	0	0	1 (0.7)	0	1 (0.2)	0	0.2 (-0.2, 0.5)
Asthma	0	1 (0.9)	0	0	0	0	0	1 (0.3)	-0.3 (-1.0, 0.3)
Vascular disorders	0	0	1 (0.5)	0	1 (0.7)	0	2 (0.3)	0	0.3 (-0.1, 0.8)
Deep vein thrombosis	0	0	1 (0.5)	0	1 (0.7)	0	2 (0.3)	0	0.3 (-0.1, 0.8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Duration is approx. 50 weeks.

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

Abbreviations: CI, confidence interval; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OTE, oteseconazole; PLB, placebo; SOC, system organ class

An analysis of nonfatal, treatment-emergent SAEs by FDA Medical Dictionary for Regulatory Activities Query (narrow) terms yielded similar results to those in [Table 39](#).

Phase 2b Trial CL-006

Four subjects in the oteseconazole arm, including Subject (b) (6) with two nonfatal, treatment-emergent SAEs (PT: abdominal pain and pancreatitis), had a total of five TEAEs. A single subject in the placebo arm had a nonfatal, treatment-emergent SAE. All TEAEs were reportedly resolved and were assessed by the Study Investigator as being unrelated to the study drug. Subject (b) (6) withdrew from the study drug due to PT: pancreatitis.

Subject narratives of all CL-006 nonfatal SAEs are found in Section [17.1.4](#) of the Appendix.

Table 39. Nonfatal, Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Supportive Phase 2 Trial 006 (ISS Population)

System Organ Class Preferred Term	Combined OTE Trial 006*	PLB Trial 006	Risk Difference OTE Trial 006 (%) (95% CI)
	N=166 n (%)	N=45 n (%)	
Gastrointestinal disorders**	1 (0.6)	0	0.6 (-0.6, 1.8)
Abdominal pain	1 (0.6)	0	0.6 (-0.6, 1.8)
Pancreatitis	1 (0.6)	0	0.6 (-0.6, 1.8)
Infections and infestations	3 (1.8)	1 (2.2)	-0.4 (-5.2, 4.3)
Appendicitis	1 (0.6)	0	0.6 (-0.6, 1.8)
Meningitis viral	1 (0.6)	0	0.6 (-0.6, 1.8)
Paronychia	0	1 (2.2)	-2.2 (-6.5, 2.1)
Pneumonia	1 (0.6)	0	0.6 (-0.6, 1.8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Duration is approx. 50 weeks.

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

** Note: Subject (b) (6) (age 36, race White) of the oteseconazole arm experienced (2) TEAE PTs abdominal pain and pancreatitis.

*Combined OTE Trial 006: Indicates following doses and durations [150 mg 12 weeks, subjects=41; 150 mg 24 weeks, subjects=42; 300 mg 12 weeks, subjects=42; 300 mg 24 weeks, subjects=41]

Complete list of SAEs by SOC and PT available in Table 9 of the STF report.

Abbreviations: CI, confidence interval; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OTE, oteseconazole; PLB, placebo; SOC, system organ class

Review of FDA specified FMQs of Trial CL-006 SAEs yielded no differences from those nonfatal, treatment-emergent SAEs listed above.

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Phase 3 Trials CL-011, CL-012, and CL-017

Five subjects (5/871; 0.57%) in the pooled phase 3 trials, four of whom were randomized to the oteseconazole arm (4/580; 0.70%) and one randomized to placebo (1/291; 0.34%), had TEAEs resulting in study drug discontinuation. Three of the four events occurring in the oteseconazole arm were assessed by the Study Investigator as being related (Subject (b) (6)/PT: dermatitis allergic) or possibly related to oteseconazole (Subject (b) (6)/PT: abdominal distension and Subject (b) (6)/PT: blister); whereas one TEAE in the oteseconazole arm resulting in study drug discontinuation was assessed as being unrelated or unlikely to be related (Subject: (b) (6))

NDA 215888
Vivjoa (oteseconazole)

(b) (6)/PT: vaginal infection) to the study drug. All subjects were reported to have recovered from the event, with the exception of one subject for whom the event outcome was missing. A single event was reported to have occurred while the subject was not actively receiving treatment (Subject (b) (6)/PT: influenza). All other subjects had been receiving study treatment at the time of the event.

Upon review of all phase 3 treatment-emergent adverse events resulting in oteseconazole discontinuation, the clinical reviewer made the following determinations: PT: vaginal infection (Subject (b) (6)) was deemed a potential treatment failure; PT: blister (Subject (b) (6)) had insufficient evidence to definitively exclude the possibility that the observed event was unrelated to oteseconazole exposure; PT: abdominal distention was determined to be possibly related to oteseconazole exposure; and PT: allergic dermatitis (Subject (b) (6)) was deemed to be definitely related to oteseconazole exposure.

Refer to Section [17.2](#) of the Appendix for narratives of all the pooled phase 3 treatment-emergent adverse events leading to discontinuation of study drug.

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Table 40. Treatment-Emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Pooled Phase 3 Safety Population, Trials CL-011, -012, and -017 (ISS)

System Organ Class Preferred Term	Trial CL-011		Trial CL-012		Trial CL-017		Risk Difference Pooled Phase 3	
	OTE N=217 n (%)	PLB N=110 n (%)	OTE N=217 n (%)	PLB N=109 n (%)	OTE N=146 n (%)	PLB N=72 n (%)	OTE Phase 3 N=580 n (%)	PLB Phase 3 N=291 n (%) (%) (95% CI)
Infections and infestations	1 (0.5)	0	0	1 (0.9)	0	0	1 (0.2)	1 (0.3) -0.2 (-0.9, 0.6)
Influenza	0	0	0	1 (0.9)	0	0	0	1 (0.3) -0.3 (-1.0, 0.3)
Vaginal infection	1 (0.5)	0	0	0	0	0	1 (0.2)	0 0.2 (-0.2, 0.5)
Skin and subcutaneous tissue disorders	0	0	1 (0.5)	0	1 (0.7)	0	2 (0.3)	0 0.3 (-0.1, 0.8)
Dermatitis allergic	0	0	0	0	1 (0.7)	0	1 (0.2)	0 0.2 (-0.2, 0.5)
Blister	0	0	1 (0.5)	0	0	0	1 (0.2)	0 0.2 (-0.2, 0.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment emergent.

Duration is approx. 50 weeks.

Notes: CL-011 (b) (6) (Oteseconazole) (PT: Vaginal infection); CL-012 (b) (6) (PT: Blister); CL-012 (b) (6) (Oteseconazole) (PT: Abdominal distention); CL-017 (b) (6) (Oteseconazole) (PT: Dermatitis allergic; In the Placebo arm: CL-012- (b) (6) (PT: Influenza)

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

Abbreviations: CI, confidence interval; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; OTE, oteseconazole; PLB, placebo; SOC, system organ class

Phase 2b CL-006

A total of two TEAEs leading to discontinuation of the study drug occurred in Trial CL-006, both of which occurred in the oteseconazole arm: Subject (b) (6) (PT: dermatitis allergic) and Subject (b) (6) in the oteseconazole 150 mg x 12 weeks arm (PT: pancreatitis), which was also described above as a nonfatal SAE. No TEAEs leading to study discontinuation occurred in the placebo arm of Trial CL-006. Refer to Section [17.2.4](#) of the Appendix for further details on these subject narratives.

7.6.5. Treatment-Emergent Adverse Events

Phase 3 Trials CL-011, CL-012, and CL-017

A total of 1,524 TEAEs (irrespective of causality) were reported in over half (56.5%; 492/871) of all subjects comprising the safety population: 55.2% (320/580) and 59.1% (172/291) in the oteseconazole and the placebo arms, respectively. The greatest numerical incidence of TEAEs in the pooled phase 3 safety population occurred under the Infections and infestations SOC (399 TEAEs) (36.6%, 212/580); followed by the Gastrointestinal disorders SOC (106 TEAEs) (12.4%, 71/580); the Reproductive system and breast disorders SOC (80 TEAEs) (10.2%, 59/580); the Nervous system disorders SOC (78 TEAEs) (9.8%, 57/580); the Investigations SOC (44 TEAEs) and the Musculoskeletal and connective tissue SOC (40 TEAEs) (6.0%, 35/580).

The most common TEAEs in the oteseconazole arm were as follows: nasopharyngitis (12.8%; 74/580); urinary tract infections (8.8%, 51/580) (PT: urinary tract infection, cystitis, *Escherichia* urinary tract infection); bacterial vaginosis (PT: bacterial vaginosis, bacterial vulvovaginitis, and vaginitis *Gardnerella*) (7.6%, 47/580); headache (headache, migraines, and sinus headache) (7.4%; 43/580); and abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness) (2.1%; 18/580). Likewise, in the placebo arm, the majority of TEAEs were coded under the Infections and infestations SOC, followed by the Reproductive system and breast disorders SOC; Gastrointestinal disorders SOC; Nervous system disorders SOC; and Musculoskeletal and connective tissue disorders SOC. Upon evaluation of all TEAEs in the oteseconazole arm, the reviewer considered the following to be adverse reactions: urinary tract infections, bacterial vaginosis, headache, nausea, abdominal pain, pyrexia, and diarrhea.

The clinical reviewer evaluated several TEAEs to determine if there were increased observations of VVC failures among subjects in both treatment arms with TEAEs coded to bacterial vaginosis (BV), urinary tract infection (UTI), STI (gonorrhea, chlamydia, genital herpes), which include signs and symptoms of vaginal irritation. None of the 4 subjects in the oteseconazole arm with a TEAE of VVC were confirmed-treatment failures; whereas, 5 of the 10 subjects in the placebo arm with TEAEs coded to the PT: vulvovaginal candidiasis and vulvovaginal mycotic infection were confirmed treatment failures.

Table 41. Treatment-Emergent Adverse Events Occurring at ≥1% Frequency in Pooled Oteseconazole Treatment Group by System Organ Class and Preferred Term/Grouped Query, Safety Population, Trials 011, 012 and 017 (ISS)

System Organ Class Preferred Term/Grouped Query	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)	Total Phase 3 N=871 n (%)	Risk Difference Pooled OTE vs. Pooled PLB (%) (95% CI)
Infections and infestations	212 (36.6)	123 (42.3)	335 (38.5)	-5.7 (-12.6, 1.2)
Nasopharyngitis/Upper respiratory tract infections	74 (12.7)	35 (12.0)	109 (12.5)	0.7 (-3.9, 5.4)
Urinary tract infections	51 (8.8)	33 (11.3)	84 (9.6)	-2.5 (-6.9, 1.8)
Bacterial vaginosis	47 (8.1)	30 (10.3)	77 (8.8)	-2.2 (-6.3, 1.9)
Sinusitis	22 (3.8)	9 (3.1)	31 (3.6)	0.7 (-1.8, 3.2)
Influenza	16 (2.8)	7 (2.4)	23 (2.6)	0.4 (-1.9, 2.6)
Herpes simplex infection	8 (1.4)	6 (2.1)	14 (1.6)	-0.7 (-2.6, 1.2)
Chlamydial infection	7 (1.2)	3 (1.0)	10 (1.1)	0.2 (-1.3, 1.6)
Bronchitis	7 (1.2)	5 (1.7)	12 (1.4)	-0.5 (-2.2, 1.2)
Rhinitis	6 (1.0)	0	6 (0.7)	1.0 (0.2, 1.9)
Gastrointestinal disorders	71 (12.2)	30 (10.3)	101 (11.6)	1.9 (-2.5, 6.3)
Nausea	21 (3.6)	7 (2.4)	28 (3.2)	1.2 (-1.1, 3.5)
Abdominal pain	18 (3.1)	10 (3.4)	28 (3.2)	-0.3 (-2.9, 2.2)
Diarrhea	12 (2.1)	7 (2.4)	19 (2.2)	-0.3 (-2.4, 1.8)
Vomiting	10 (1.7)	5 (1.7)	15 (1.7)	0.0 (-1.8, 1.8)
Reproductive system and breast disorders	59 (10.2)	40 (13.7)	99 (11.4)	-3.6 (-8.2, 1.1)
Menorrhagia/metrorrhagia	18 (3.1)	6 (2.1)	24 (2.8)	1.0 (-1.1, 3.2)
Vulvovaginal pruritus	12 (2.1)	11 (3.8)	23 (2.6)	-1.7 (-4.2, 0.8)
Vulvovaginal irritation	10 (1.7)	5 (1.7)	15 (1.7)	0.0 (-1.8, 1.8)
Nervous system disorders	57 (9.8)	25 (8.6)	82 (9.4)	1.2 (-2.8, 5.3)
Headache	43 (7.4)	21 (7.2)	64 (7.3)	0.2 (-3.5, 3.9)
Musculoskeletal and connective tissue disorders	35 (6.0)	14 (4.8)	49 (5.6)	1.2 (-1.9, 4.4)
Back pain	10 (1.7)	9 (3.1)	19 (2.2)	-1.4 (-3.6, 0.9)
Investigations	32 (5.5)	16 (5.5)	48 (5.5)	0.0 (-3.2, 3.2)
Blood creatine phosphokinase increased	11 (1.9)	5 (1.7)	16 (1.8)	0.2 (-1.7, 2.0)
General disorders and administration site conditions	31 (5.3)	13 (4.5)	44 (5.1)	0.9 (-2.1, 3.9)
Pyrexia	13 (2.2)	8 (2.7)	21 (2.4)	-0.5 (-2.7, 1.7)
Fatigue	6 (1.0)	1 (0.3)	7 (0.8)	0.7 (-0.4, 1.8)

System Organ Class Preferred Term/Grouped Query	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)	Total Phase 3 N=871 n (%)	Risk Difference Pooled OTE vs. Pooled PLB (%) (95% CI)
Skin and subcutaneous tissue disorders	31 (5.3)	17 (5.8)	48 (5.5)	-0.5 (-3.8, 2.8)
Acne	7 (1.2)	1 (0.3)	8 (0.9)	0.9 (-0.3, 2.0)
Renal and urinary disorders	16 (2.8)	6 (2.1)	22 (2.5)	0.7 (-1.4, 2.8)
Dysuria	7 (1.2)	1 (0.3)	8 (0.9)	0.9 (-0.3, 2.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Duration is approx. 50 weeks.

The analysis included all TEAEs by GQ and PT $\geq$ 1% as found in the pooled oteseconazole treatment group.

Total = total combined subjects with events occurring in pooled OTE and pooled PLB in the Phase 3 trials (011, 012 and 017).

*Subjects who experienced more than one TEAE in the GQ: VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6)

(b) (6) VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-011 (b) (6); VMT-VT-1161-CL-011 (b) (6); VMT-VT-1161-CL-011 (b) (6) VMT-VT-1161-CL-012 (b) (6) VMT-VT-1161-CL-012 (b) (6) VMT-VT-1161-CL-012 (b) (6) VMT-VT-1161-CL-012 (b) (6); VMT-VT-1161-CL-012 (b) (6); VMT-VT-1161-CL-012 (b) (6)

VMT-VT-1161-CL-012 (b) (6) VMT-VT-1161-CL-017 (b) (6) VMT-VT-1161-CL-017 (b) (6)

Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.

Notes: GQ term **Abdominal pain** includes the following terms; abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper; abdominal tenderness; GQ term: **Acne** includes the following terms: Acne, Acne cystic; GQ term **Bacterial vaginosis** includes the following terms: Bacterial vaginosis; Bacterial vulvovaginitis, Vaginitis Gardnerella; GQ term **Chlamydial infection** includes the following terms: Chlamydial cervicitis; GQ term includes the following terms **Headache** includes the following terms: Headache, migraines, sinus headaches; GQ term **Herpes Simplex infection** includes the following terms Genital herpes; genital herpes simplex; herpes simplex; GQ term **Menorrhagia/metrorrhagia** includes the following terms: menometrorrhagia; menorrhagia; metrorrhagia; genital hemorrhage; uterine hemorrhage; vaginal hemorrhage; GQ term **Nasopharyngitis/Upper respiratory tract infections** includes the following terms: nasopharyngitis; pharyngitis; pharyngitis streptococcal; respiratory tract congestion; respiratory tract infection viral, upper respiratory tract infection; viral pharyngitis; viral upper respiratory tract infection; GQ term **Rhinitis** includes the following terms: Rhinitis; Rhinitis allergic; GQ term **Sinusitis** includes the following terms: Acute sinusitis, sinusitis, sinusitis bacterial; GQ term **Urinary tract infection** includes the following terms: cystitis; Escherichia urinary tract infection; urinary tract infection; GQ term **Vulvovaginal irritation** includes the following terms; vulvovaginal burning sensation; vulvovaginal discomfort; vulvovaginal pain

Abbreviations: CI, confidence interval; GQ, Grouped Query; N, number of patients in treatment arm; n, number of patients with adverse event.

Phase 2b Trial CL-006

Trial CL-006 was a dose range-finding multicenter, randomized, double-blind, placebo-controlled parallel-group efficacy, safety, tolerability and PK trial in which eligible prospective participants were randomized into placebo or one of four oteseconazole treatment arms.

A total of 215 participants comprised the ITT population, four of whom were not included in the safety population of 211 subjects and did not receive study drug.

A tabular summary ([Table 170](#)) of the phase 2b safety findings are described in the Appendix. The safety profile in Trial CL-006 reflects and supports the safety profile demonstrated in the combined phase 3 trials, where the most common TEAEs in the oteseconazole arm were found under the Infections and infestations SOC (e.g., BV, UTI, nasopharyngitis, and sinusitis); the Gastrointestinal disorders SOC (e.g., nausea, abdominal pain, abdominal distension, diarrhea); and the Reproductive system and breast disorders SOC (vulvovaginal irritation, menorrhagia/metrorrhagia).

7.6.6. Laboratory Findings

Pooled Phase 3 Trials CL-011, CL-012, and CL-017

Complete Blood Count

[Table 42](#) illustrates there were no imbalances between study arms in the key complete blood count parameters (e.g., white blood cells, hemoglobin and hematocrit, and platelets) in any of the individual three phase 3 trials or in the pooled phase 3 trials which merited further investigation by the clinical reviewer. The same is true of the key hematologic parameters in the supportive phase 2b trial (Trial CL-006).

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Table 42. Patients With One or More Hematology Analyte Values Outside Specified Levels, Safety Population, Trials CL-017, -012, -011

Laboratory Parameter	Trial CL-017		Trial CL-012		Trial CL-011		Pooled		Risk Difference Pooled Phase 3 (%) (95% CI)
	OTE N=146 n (%)	PLB N=72 n (%)	OTE N=217 n (%)	PLB N=110 n (%)	OTE N=217 n (%)	PLB N=109 n (%)	OTE Phase 3 N=580 n (%)	PLB Phase 3 N=291 n (%)	
Complete blood count									
WBC, low (cells/uL)									
Level 1 (<3500)	10/142 (7.0)	2/69 (2.9)	12/211 (5.7)	5/105 (4.8)	9/215 (4.2)	1/109 (0.9)	31/568 (5.5)	8/283 (2.8)	2.6 (-0.1, 5.3)
Level 2 (<3000)	2/142 (1.4)	1/69 (1.4)	4/211 (1.9)	1/105 (1.0)	2/215 (0.9)	1/109 (0.9)	8/568 (1.4)	3/283 (1.1)	0.3 (-1.2, 1.9)
Level 3 (<1000)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	0/215 (0)	0/109 (0)	0/568 (0)	0/283 (0)	0 (0, 0)
WBC, high (cells/uL)									
Level 1 (>10800)	12/142 (8.5)	8/69 (11.6)	18/211 (8.5)	15/105 (14.3)	19/215 (8.8)	8/109 (7.3)	49/568 (8.6)	31/283 (11.0)	-2.3 (-6.6, 2.0)
Level 2 (>13000)	3/142 (2.1)	3/69 (4.3)	2/211 (0.9)	5/105 (4.8)	2/215 (0.9)	0/109 (0)	7/568 (1.2)	8/283 (2.8)	-1.6 (-3.7, 0.5)
Level 3 (>15000)	1/142 (0.7)	0/69 (0)	1/211 (0.5)	2/105 (1.9)	0/215 (0)	0/109 (0)	2/568 (0.4)	2/283 (0.7)	-0.4 (-1.4, 0.7)
Hemoglobin, low (g/dL)									
Level 1 (NA)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	1/215 (0.5)	0/109 (0)	1/568 (0.2)	0/283 (0)	0.2 (-0.2, 0.5)
Level 2 (>1.5 dec. from baseline)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	1/215 (0.5)	0/109 (0)	1/568 (0.2)	0/283 (0)	0.2 (-0.2, 0.5)
Level 3 (>2 dec. from baseline)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	0/215 (0)	0/109 (0)	0/568 (0)	0/283 (0)	0 (0, 0)
Hemoglobin, high (g/dL)									
Level 1 (NA)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	0/215 (0)	0/109 (0)	0/568 (0)	0/283 (0)	0 (0, 0)
Level 2 (>2X baseline)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	0/215 (0)	0/109 (0)	0/568 (0)	0/283 (0)	0 (0, 0)
Level 3 (>3X baseline)	0/142 (0)	0/69 (0)	0/211 (0)	0/105 (0)	0/215 (0)	0/109 (0)	0/568 (0)	0/283 (0)	0 (0, 0)
Platelets, low (cells/uL)									
Level 1 (<140000)	1/141 (0.7)	0/69 (0)	6/211 (2.8)	3/105 (2.9)	2/215 (0.9)	2/109 (1.8)	9/567 (1.6)	5/283 (1.8)	-0.2 (-2.0, 1.7)
Level 2 (<125000)	0/141 (0)	0/69 (0)	1/211 (0.5)	0/105 (0)	2/215 (0.9)	1/109 (0.9)	3/567 (0.5)	1/283 (0.4)	0.2 (-0.7, 1.1)
Level 3 (<1e+05)	0/141 (0)	0/69 (0)	0/211 (0)	0/105 (0)	1/215 (0.5)	0/109 (0)	1/567 (0.2)	0/283 (0)	0.2 (-0.2, 0.5)

Source: adlb.xpt; Software: R

Abbreviations: OTE, oteseconazole; PLB, placebo; NA, not applicable; WBC, white blood cell.

Chemistries

Similarly, outside of the below-described imbalances in creatine phosphokinase (CPK) elevations, there were no significant electrolyte imbalances between the two treatment arms in any of the individual three phase 3 trials or in the pooled phase 3 trials which merited further investigation by the clinical reviewer ([Table 43](#)). Likewise, outside of the observed CPK imbalances in the oteseconazole arm, there were no significant electrolyte/ chemistry imbalances in the supportive Phase 2b trial (Trial CL-006).

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Table 43. Electrolyte/Chemistry Findings in the Phase 3 Trials

Laboratory Parameter (mEq/L)	Trial CL-017		Trial CL-012		Trial CL-011		Pooled		RD Pooled Phase 3 (%) (95% CI)
	OTE N=146 n (%)	PLB N=72 n (%)	OTE N=217 n (%)	PLB N=110 n (%)	OTE N=217 n (%)	PLB N=109 n (%)	OTE Phase 3 N=580 n (%)	PLB Phase 3 N=291 n (%)	
Sodium, low									
Level 1 (<134)	5/142 (3.5)	3/68 (4.4)	4/212 (1.9)	0/106 (0)	2/215 (0.9)	3/109 (2.8)	11/569 (1.9)	6/283 (2.1)	-0.2 (-2.2, 1.8)
Level 2 (<132)	0/142 (0)	2/68 (2.9)	0/212 (0)	0/106 (0)	1/215 (0.5)	2/109 (1.8)	1/569 (0.2)	4/283 (1.4)	-1.2 (-2.7, 0.2)
Level 3 (<125)	0/142 (0)	1/68 (1.5)	0/212 (0)	0/106 (0)	0/215 (0)	0/109 (0)	0/569 (0)	1/283 (0.4)	-0.4 (-1.0, 0.3)
Sodium, high									
Level 1 (>144)	7/142 (4.9)	3/68 (4.4)	14/212 (6.6)	12/106 (11.3)	19/215 (8.8)	9/109 (8.3)	40/569 (7.0)	24/283 (8.5)	-1.5 (-5.3, 2.4)
Level 2 (>150)	0/142 (0)	1/68 (1.5)	0/212 (0)	0/106 (0)	1/215 (0.5)	0/109 (0)	1/569 (0.2)	1/283 (0.4)	-0.2 (-0.9, 0.6)
Level 3 (>155)	0/142 (0)	0/68 (0)	0/212 (0)	0/106 (0)	0/215 (0)	0/109 (0)	0/569 (0)	0/283 (0)	0 (0, 0)
Chloride, low									
Level 1 (<95)	3/142 (2.1)	2/68 (2.9)	3/212 (1.4)	0/106 (0)	0/215 (0)	2/109 (1.8)	6/569 (1.1)	4/283 (1.4)	-0.4 (-2.0, 1.3)
Level 2 (<88)	0/142 (0)	0/68 (0)	1/212 (0.5)	0/106 (0)	0/215 (0)	0/109 (0)	1/569 (0.2)	0/283 (0)	0.2 (-0.2, 0.5)
Level 3 (<80)	0/142 (0)	0/68 (0)	0/212 (0)	0/106 (0)	0/215 (0)	0/109 (0)	0/569 (0)	0/283 (0)	0 (0, 0)
Chloride, high									
Level 1 (>108)	1/142 (0.7)	1/68 (1.5)	3/212 (1.4)	1/106 (0.9)	3/215 (1.4)	4/109 (3.7)	7/569 (1.2)	6/283 (2.1)	-0.9 (-2.8, 1.0)
Level 2 (>112)	0/142 (0)	0/68 (0)	0/212 (0)	0/106 (0)	0/215 (0)	1/109 (0.9)	0/569 (0)	1/283 (0.4)	-0.4 (-1.0, 0.3)
Level 3 (>115)	0/142 (0)	0/68 (0)	0/212 (0)	0/106 (0)	0/215 (0)	0/109 (0)	0/569 (0)	0/283 (0)	0 (0, 0)
Bicarbonate, low									
Level 1 (<20)	32/142 (22.5)	13/68 (19.1)	38/212 (17.9)	20/106 (18.9)	52/215 (24.2)	17/109 (15.6)	122/569 (21.4)	50/283 (17.7)	3.8 (-1.8, 9.4)
Level 2 (<18)	8/142 (5.6)	4/68 (5.9)	6/212 (2.8)	6/106 (5.7)	15/215 (7.0)	3/109 (2.8)	29/569 (5.1)	13/283 (4.6)	0.5 (-2.5, 3.5)
Level 3 (<15)	0/142 (0)	1/68 (1.5)	0/212 (0)	0/106 (0)	1/215 (0.5)	0/109 (0)	1/569 (0.2)	1/283 (0.4)	-0.2 (-0.9, 0.6)
Bicarbonate, high									
Level 1 (NA)	0/142 (0)	0/68 (0)	1/212 (0.5)	0/106 (0)	1/215 (0.5)	0/109 (0)	2/569 (0.4)	0/283 (0)	0.4 (-0.1, 0.8)
Level 2 (NA)	0/142 (0)	0/68 (0)	1/212 (0.5)	0/106 (0)	1/215 (0.5)	0/109 (0)	2/569 (0.4)	0/283 (0)	0.4 (-0.1, 0.8)
Level 3 (>30)	0/142 (0)	0/68 (0)	1/212 (0.5)	0/106 (0)	1/215 (0.5)	0/109 (0)	2/569 (0.4)	0/283 (0)	0.4 (-0.1, 0.8)

Source: adlb.xpt; Software: R
Abbreviations: NA, not applicable; OTE, oteseconazole; PLB, placebo; RD, risk difference

Creatine Phosphokinase

An imbalance in CPK elevations was observed between subjects treated with oteseconazole when compared with those receiving placebo in the phase 3 and supportive phase 2 trials. It is noted that a 2:1 randomization ratio was used in the three phase 3 trials (Trials CL-011, CL-012, and CL-017), whereas a 1:1:1:1 randomization scheme was used for the phase 2b (Trial CL-006) (4 dosing cohorts received oteseconazole and a single cohort received placebo).

The clinical reviewer used the DAIDS toxicity grading table to detect any significant maximal post-baseline changes in CPK values compared with baseline CPK values among the 561 and the 275 randomized subjects in the oteseconazole and placebo arms, respectively, with baseline and postbaseline CPK values in the combined phase 3 trials. The analysis identified 6 of 561 (1.1%) versus 1 of 275 subjects (0.4%), respectively, with normal baseline CPK (Grade 0) values who developed Grade 3 (severe) maximal post-baseline CPK elevations of 10 to <20 x upper limit of normal (ULN) (with the ULN being 192 U/L). In addition, there were a total of 5 of 561 (0.9%) oteseconazole subjects versus 1 of 275 (0.4%) placebo subjects, respectively, with normal baseline CPK values who developed Grade 4 (potentially life-threatening) post-baseline CPK elevations of ≥ 20 x ULN (Table 44). In most instances, the Applicant did not identify the observed maximal post-baseline CPK elevations as TEAEs. Narratives of these subjects can be found in Section [17.4](#) in the Appendix, and a more detailed discussion of the observed CPK elevations can be found under Section [7.7.2](#) Key Risk Review Issues.

In light of the relationship between CPK elevations (specifically rhabdomyolysis) and such electrolyte disorders as hypokalemia or hyperkalemia, hypophosphatemia, and hypocalcemia, the reviewer directed special attention towards the evaluation of potassium (K^+), phosphate, and calcium (Ca^{2+}) and assessed maximal/minimal changes from baseline for these laboratory parameters. Upon investigation, no notable electrolyte imbalances between the oteseconazole arm or the placebo arm were appreciated. Importantly, there were no observed baseline imbalances of hypokalemia, hypophosphatemia, or hypocalcemia that could explain the observed CPK elevations. There were also no elevations in the lab parameters associated with observed CPK elevations (e.g., creatinine)

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Table 44. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Phase 3 Trials 011, 012, 017 (ISS)

Laboratory Toxicity Parameter	Baseline	Maximal Postbaseline Toxicity Grade		Trial CL-011		Trial CL-012		Trial CL-017		Pooled	
	Grade	OTE N=217 [n/Ns (%)]	PLB N=109 [n/Ns (%)]	OTE N=217 [n/Ns (%)]	PLB N=110 [n/Ns (%)]	OTE N=146 [n/Ns (%)]	FLU/PLB N=72 [n/Ns (%)]	OTE Phase 3 N=580 [n/Ns (%)]	PLB Phase 3 N=291 [n/Ns (%)]		
Creatine kinase (U/L), high	Grade 0	Grade 0 (LLN to <3x ULN)	197/209 (94.3)	90/101 (89.1)	202/214 (94.4)	99/108 (91.7)	133/138 (96.4)	62/66 (93.9)	532/561 (94.8)	251/275 (91.3)	
	Grade 0	Grade 1 (3 to <6x ULN)	6/209 (2.9)	8/101 (7.9)	6/214 (2.8)	7/108 (6.5)	1/138 (0.7)	3/66 (4.5)	13/561 (2.3)	18/275 (6.5)	
		Grade 2 (6 to <10x ULN)	1/209 (0.5)	2/101 (2)	3/214 (1.4)	1/108 (0.9)	1/138 (0.7)	0/66 (0)	5/561 (0.9)	3/275 (1.1)	
		Grade 3 (10 to <20x ULN)	2/209 (1)	1/101 (1)	3/214 (1.4)	0/108 (0)	1/138 (0.7)	0/66 (0)	6/561 (1.1)	1/275 (0.4)	
		Grade 4 (≥20x ULN)	3/209 (1.4)	0/101 (0)	0/214 (0)	1/108 (0.9)	2/138 (1.4)	0/66 (0)	5/561 (0.9)	1/275 (0.4)	
		Grade 1	Grade 0 (LLN to <3x ULN)	1/1 (100)	1/2 (50)	0	0	1/1 (100)	1/2 (50)	2/2 (100)	2/4 (50)
	Grade 1 (3 to <6x ULN)		0/1 (0)	1/2 (50)	0	0	0/1 (0)	1/2 (50)	0/2 (0)	2/4 (50)	
	Grade 2	Grade 0 (LLN to <3x ULN)	0	0	0	0	1/1 (100)	0	1/1 (100)	0	
	Grade 3	Grade 0 (LLN to <3x ULN)	0	0	1/1 (100)	0	0	0	1/1 (100)	0	
	Missing	Grade 0 (LLN to <3x ULN)	0	0	0	0	1/2 (50)	0	1/2 (50)	0	
	Missing	Grade 1 (3 to <6x ULN)	0	0	0	0	1/2 (50)	0	1/2 (50)	0	

Source: adlb.xpt; Software: R; Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events.(version 2.1, July 2017)

Duration is approximately 50 weeks.

Abbreviations: ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; ULN, upper limit of normal; OTE, oteseconazole; PLB, placebo

Table 45. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Post-Baseline Laboratory Toxicities, Safety Population, Phase 2b Trial 006 (ISS)

Lab Parameter	Baseline Toxicity Grade	Maximal Post-Baseline Toxicity Grade	1050 mg/150 mg	1050 mg/150 mg	2100 mg/300 mg	2100 mg/300 mg	Placebo
			11 wks	23 wks	11 wks	23 wks	
			Oteseconazole N=41 [n/Ns (%)]	Oteseconazole N=42 [n/Ns (%)]	Oteseconazole N=42 [n/Ns (%)]	Oteseconazole N=41 [n/Ns (%)]	N=45 [n/Ns (%)]
Creatine Kinase (U/L), High	Grade 0	Grade 0 (LLN to <3x ULN)	36/41 (87.8)	41/41 (100)	35/40 (87.5)	35/38 (92.1)	43/45 (95.6)
		Grade 1 (3 to <6x ULN)	1/41 (2.4)	0/41 (0)	2/40 (5)	2/38 (5.3)	2/45 (4.4)
		Grade 2 (6 to <10x ULN)	2/41 (4.9)	0/41 (0)	0/40 (0)	0/38 (0)	0/45 (0)
		Grade 3 (10 to <20x ULN)	1/41 (2.4)	0/41 (0)	0/40 (0)	0/38 (0)	0/45 (0)
		Grade 4 (≥20x ULN)	1/41 (2.4)	0/41 (0)	3/40 (7.5)	1/38 (2.6)	0/45 (0)
	Grade 1	Grade 2 (6 to <10x ULN)	0	0	0	1/2 (50)	0
		Grade 3 (10 to <20x ULN)	0	0	0	1/2 (50)	0
	Grade 2	Grade 1 (3 to <6x ULN)	0	0	1/1 (100)	0	0

Source: adlb.xpt; Software: R; Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Duration is approximately 50 weeks.

Abbreviations: ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; ULN, upper limit of normal.

As illustrated in the table above, in the smaller phase 2b study, CL-006, a single subject in the oteseconazole 1050 mg/150 mg x 11 weeks arm with a normal baseline CPK value developed Grade 3, 10 to <20x ULN (1/160, 0.6%) maximal post-baseline CPK elevation and 5 out of a total 160 (3.1%) subjects across 3 of the 4 oteseconazole arms developed Grade 4 (≥ 20 x ULN) maximal post-baseline CPK values. No subjects in the placebo arm demonstrated either Grade 3 or Grade 4 CPK elevations. Narratives of these subjects can be found in Section [17.4](#) of the Appendix and a more detailed discussion of the observed CPK elevations can be found under Section [7.7.2](#).

Hepatic Function Tests

Hepatic injury, transaminase elevations, and cholestasis are well-known azole class-associated adverse reactions. As such, the reviewer evaluated graded maximal post baseline analyses for the transaminases; alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Analysis of specific transaminases did not identify any signals indicative of hepatic failure. However, a consistent pattern of parallel, transient AST elevations appeared to emerge when evaluating transaminase elevations in the context of CPK elevations. Concomitant elevations in ALT were not consistently observed in subjects with CPK elevations. Shift tables generated to evaluate maximal post-baseline changes for total and direct bilirubin demonstrated no concerning safety signals to suggest the potential for cholestatic injury.

Further discussion on increased transaminases co-occurring with CPK elevations is found separately under Section [7.7.2](#). Subject narratives can be found in Sections [17.3.1](#) and [17.4](#) in the Appendix.

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Table 46. Alanine Aminotransferase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS)

Laboratory Parameter	Baseline Toxicity Grade	Maximal Postbaseline Toxicity Grade	Trial CL-011		Trial CL-012		Trial CL-017		Pooled	
			OTE N=217 [n/Ns (%)]	PLB N=109 [n/Ns (%)]	OTE N=217 [n/Ns (%)]	PLB N=110 [n/Ns (%)]	OTE N=146 [n/Ns (%)]	FLU/PLB N=72 [n/Ns (%)]	OTE Phase 3 N=580 [n/Ns (%)]	PLB Phase 3 N=291 [n/Ns (%)]
Alanine amino-transferase (U/L), High	Grade 0	Grade 0 (<1.25x ULN)	186/206 (90.3)	95/104 (91.3)	196/213 (92)	101/109 (92.7)	129/138 (93.5)	60/64 (93.8)	511/557 (91.7)	256/277 (92.4)
		Grade 1 (1.25 to <2.5x ULN)	18/206 (8.7)	7/104 (6.7)	16/213 (7.5)	5/109 (4.6)	7/138 (5.1)	3/64 (4.7)	41/557 (7.4)	15/277 (5.4)
		Grade 2 (2.5 to <5.0x ULN)	2/206 (1)	2/104 (1.9)	0/213 (0)	3/109 (2.8)	2/138 (1.4)	1/64 (1.6)	4/557 (0.7)	6/277 (2.2)
		Grade 3 (5.0 to <10.0x ULN)	0/206 (0)	0/104 (0)	1/213 (0.5)	0/109 (0)	0/138 (0)	0/64 (0)	1/557 (0.2)	0/277 (0)
	Grade 1	Grade 0 (<1.25x ULN)	2/5 (40)	1/1 (100)	1/1 (100)	0	0/2 (0)	2/4 (50)	3/8 (37.5)	3/5 (60)
		Grade 1 (1.25 to <2.5x ULN)	2/5 (40)	0/1 (0)	0/1 (0)	0	1/2 (50)	2/4 (50)	3/8 (37.5)	2/5 (40)
		Grade 2 (2.5 to <5.0x ULN)	1/5 (20)	0/1 (0)	0/1 (0)	0	1/2 (50)	0/4 (0)	2/8 (25)	0/5 (0)
	Grade 2	Grade 0 (<1.25x ULN)	0/1 (0)	1/1 (100)	1/1 (100)	0	0	0	1/2 (50)	1/1 (100)
		Grade 1 (1.25 to <2.5x ULN)	1/1 (100)	0/1 (0)	0/1 (0)	0	0	0	1/2 (50)	0/1 (0)
	Missing	Grade 0 (<1.25x ULN)	0	0	0	0	2/2 (100)	0	2/2 (100)	0

Source: adlb.xpt; Software: R

Duration is approximately 50 weeks.

Patients Outliers: Patients with alanine aminotransferase (U/L) range of 5-30 (presented as subject ID and treatment): VMT-VT-1161-CL-017 (b) (6) Oteseconazole; VMT-VT-1161-CL-017 (b) (6)

Placebo

Abbreviations: ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; OTE, oteseconazole; PLB, placebo; ULN, upper limit of normal.

Table 47. Aspartate Aminotransferase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS)

Laboratory Parameter	Baseline Toxicity Grade	Maximal Postbaseline Toxicity Grade	Trial CL-011		Trial CL-012		Trial CL-017		Pooled	
			OTE N=217 [n/Ns (%)]	PLB N=109 [n/Ns (%)]	OTE N=217 [n/Ns (%)]	PLB N=110 [n/Ns (%)]	OTE N=146 [n/Ns (%)]	FLU/PLB N=72 [n/Ns (%)]	OTE Phase 3 N=580 [n/Ns (%)]	PLB Phase 3 N=291 [n/Ns (%)]
Aspartate amino-transferase (U/L), High	Grade 0	Grade 0 (<1.25x ULN)	191/209 (91.4)	94/104 (90.4)	191/213 (89.7)	103/109 (94.5)	131/139 (94.2)	59/63 (93.7)	513/561 (91.4)	256/276 (92.8)
		Grade 1 (1.25 to <2.5x ULN)	15/209 (7.2)	9/104 (8.7)	19/213 (8.9)	5/109 (4.6)	5/139 (3.6)	4/63 (6.3)	39/561 (7)	18/276 (6.5)
		Grade 2 (2.5 to <5.0x ULN)	3/209 (1.4)	1/104 (1)	3/213 (1.4)	1/109 (0.9)	1/139 (0.7)	0/63 (0)	7/561 (1.2)	2/276 (0.7)
	Grade 1	Grade 3 (5.0 to <10.0x ULN)	0/209 (0)	0/104 (0)	0/213 (0)	0/109 (0)	2/139 (1.4)	0/63 (0)	2/561 (0.4)	0/276 (0)
		Grade 0 (<1.25x ULN)	2/3 (66.7)	2/2 (100)	1/1 (100)	0	0/1 (0)	3/5 (60)	3/5 (60)	5/7 (71.4)
		Grade 1 (1.25 to <2.5x ULN)	0/3 (0)	0/2 (0)	0/1 (0)	0	1/1 (100)	2/5 (40)	1/5 (20)	2/7 (28.6)
	Grade 2	Grade 2 (2.5 to <5.0x ULN)	1/3 (33.3)	0/2 (0)	0/1 (0)	0	0/1 (0)	0/5 (0)	1/5 (20)	0/7 (0)
		Grade 0 (<1.25x ULN)	0	0	1/1 (100)	0	0	0	1/1 (100)	0
	Missing	Grade 0 (<1.25x ULN)	0	0	0	0	2/2 (100)	0	2/2 (100)	0

Source: adlb.xpt; Software: R

Duration is approximately 50 weeks.

Abbreviations: FLU, fluconazole; ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; OTE, oteseconazole; PLB, placebo; ULN, upper limit of normal

Table 48. Alkaline Phosphatase (U/L) Shifts From Baseline for Graded Maximal Postbaseline Laboratory Toxicities, Safety Population, Trials 011, 012, 017 (ISS)

Laboratory Parameter	Baseline Toxicity Grade	Maximal Postbaseline Toxicity Grade	Trial CL-011		Trial CL-012		Trial CL-017		Pooled	
			OTE N=217 [n/Ns (%)]	PLB N=109 [n/Ns (%)]	OTE N=217 [n/Ns (%)]	PLB N=110 [n/Ns (%)]	OTE N=146 [n/Ns (%)]	FLU/PLB N=72 [n/Ns (%)]	OTE Phase 3 N=580 [n/Ns (%)]	PLB Phase 3 N=291 [n/Ns (%)]
Alkaline Phosphatase (U/L), High	Grade 0	Grade 0 (<1.25x ULN)	208/211 (98.6)	102/104 (98.1)	213/214 (99.5)	108/109 (99.1)	137/139 (98.6)	67/68 (98.5)	558/564 (98.9)	277/281 (98.6)
		Grade 1 (1.25 to <2.5x ULN)	3/211 (1.4)	2/104 (1.9)	1/214 (0.5)	1/109 (0.9)	1/139 (0.7)	1/68 (1.5)	5/564 (0.9)	4/281 (1.4)
		Grade 2 (2.5 to <5.0x ULN)	0/211 (0)	0/104 (0)	0/214 (0)	0/109 (0)	1/139 (0.7)	0/68 (0)	1/564 (0.2)	0/281 (0)
	Grade 1	Grade 0 (<1.25x ULN)	1/1 (100)	1/2 (50)	0/1 (0)	0	0/2 (0)	0	1/4 (25)	1/2 (50)
		Grade 1 (1.25 to <2.5x ULN)	0/1 (0)	1/2 (50)	1/1 (100)	0	2/2 (100)	0	3/4 (75)	1/2 (50)
	Missing	Grade 0 (<1.25x ULN)	0	0	0	0	1/1 (100)	0	1/1 (100)	0

Source: adlb.xpt; Software: R

Duration is approximately 50 weeks.

Patients Outliers: Patients with alkaline phosphatase (U/L) <187 (presented as subject ID and treatment): VMT-VT-1161-CL-011 (b) (6) Oteseconazole; VMT-VT-1161-CL-017 (b) (6)

Oteseconazole; VMT-VT-1161-CL-017 (b) (6) Placebo

Abbreviations: ISS, integrated summary of safety; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; LLN, lower limit of normal; OTE, oteseconazole; PLB, placebo; ULN, upper limit of normal

Phase 2b Trial CL-006

There were no significant laboratory differences observed in the phase 2b Trial CL-006 than those observed in the combined phase 3 trials. However, a shift table of maximal post-baseline CPK changes relative to baseline values is found below.

As illustrated in the table, a single subject receiving oteseconazole (150 mg x 3 months) with a Grade 0 (normal) baseline CPK value developed a Grade 3 maximal post-baseline CPK elevation (10 to < 20 x ULN) versus no such subjects in the placebo arm. Similarly, there were five oteseconazole treated subjects with Grade 0 (normal) CPK baseline values who developed Grade 4 (≥ 20 x ULN) maximal post-baseline CPK values: 1 in the oteseconazole 150 mg x 3 months arm; 3 in the oteseconazole 300-mg x 3 months; and 1 in the oteseconazole 300 mg x 6 months arm versus no subjects in the placebo arm or in the oteseconazole 150-mg x 6 months arm. The Applicant has suggested that the observed imbalance is attributable to differences in the randomization scheme. However, while there were no Grade 3 or 4 CPK elevations in the placebo arm, there were a total of 6 in the oteseconazole exposed subjects, with 4 of these 6 occurring in the 300-mg arm. This suggests that at the higher 300-mg dose there may have been a more pronounced dose correlation between oteseconazole and CPK laboratory elevations.

Narratives of subjects with observed CPK elevations in Trial CL-006 can be found in Sections [7.7.2](#) and [17.4.4](#) of the Appendix.

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Table 49. Creatine Kinase (U/L) Shifts From Baseline for Graded Maximal Post-Baseline Laboratory Toxicities, Safety Population, Trial 006 (ISS)

Laboratory Parameter	Baseline Toxicity Grade	Maximal Postbaseline Toxicity Grade	1050 mg/150 mg	1050 mg/150 mg	2100 mg/300 mg	2100 mg/300 mg	Placebo
			11 wks	23 wks	11 wks	23 wks	
			Oteseconazole	Oteseconazole	Oteseconazole	Oteseconazole	
			N=41	N=42	N=42	N=41	N=45
			[n/Ns (%)]	[n/Ns (%)]	[n/Ns (%)]	[n/Ns (%)]	[n/Ns (%)]
Creatine kinase (U/L), High	Grade 0	Grade 0 (LLN to <3x ULN)	36/41 (87.8)	41/41 (100)	35/40 (87.5)	35/38 (92.1)	43/45 (95.6)
		Grade 1 (3 to <6x ULN)	1/41 (2.4)	0/41 (0)	2/40 (5)	2/38 (5.3)	2/45 (4.4)
		Grade 2 (6 to <10x ULN)	2/41 (4.9)	0/41 (0)	0/40 (0)	0/38 (0)	0/45 (0)
		Grade 3 (10 to <20x ULN)	1/41 (2.4)	0/41 (0)	0/40 (0)	0/38 (0)	0/45 (0)
		Grade 4 (≥20x ULN)	1/41 (2.4)	0/41 (0)	3/40 (7.5)	1/38 (2.6)	0/45 (0)
	Grade 1	Grade 2 (6 to <10x ULN)	0	0	0	1/2 (50)	0
		Grade 3 (10 to <20x ULN)	0	0	0	1/2 (50)	0
	Grade 2	Grade 1 (3 to <6x ULN)	0	0	1/1 (100)	0	0

Source: adlb.xpt; Software: R

Duration is approximately 50 weeks.

Abbreviations: ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; ULN, upper limit of normal

Electrocardiogram

There were no significant maximal post-baseline changes in the PR interval or heart rate from baseline values in the phase 3 trials.

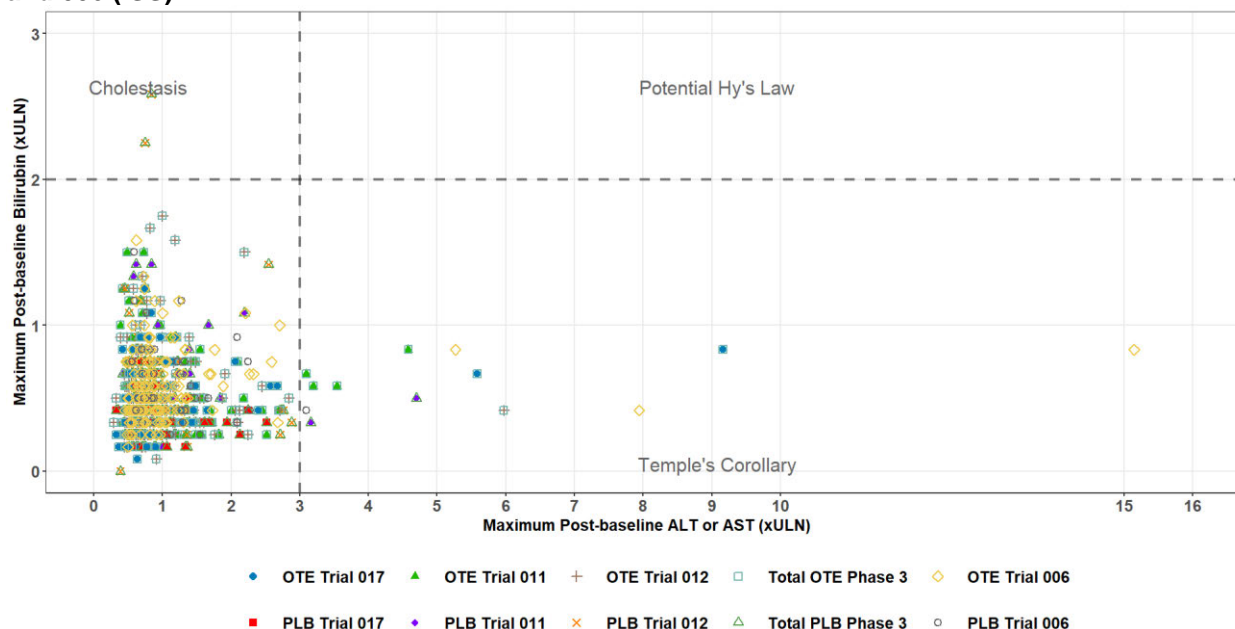
7.6.7. Additional Safety Analyses

7.6.7.1. Adverse Events of Special Interest

Hepatotoxicity—Evaluation for Hy’s Law and Temple’s Corollary Cases

The review team performed an analysis to identify any potential Hy’s law and/or Temple’s corollary cases and to assess the potential for oteseconazole-induced hepatic injury. While no subjects in the pooled phase 3 or phase 2b trials fulfilled Hy’s law criteria, there were, however, 10 subjects in the oteseconazole arm and 3 in the placebo arm who appeared to meet criteria for Temple’s corollary, defined as having a maximum postbaseline total bilirubin less than 2x ULN and having a maximum postbaseline ALT or AST equal to or exceeding 3x ULN. Transaminase elevations observed to be 10x – 15x ULN were most often associated with CPK elevations.

Figure 5. Drug-Induced Liver Injury Case Screening Plot, Safety Population, Trials 017, 012, 011 and 006 (ISS)*



Source: adlb.xpt; Software: R

Each data point represents at least one visit (from a patient) with both ALT/AST and total bilirubin values in the postbaseline period. A potential Hy’s Law case was defined as having a maximum postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after maximum postbaseline ALT or AST equal to or exceeding 3X ULN, without findings of cholestasis (defined as ALP <2X ULN). A Temple’s Corollary case was defined as having a maximum postbaseline total bilirubin less than 2X ULN and maximum postbaseline ALT or AST equal to or exceeding 3X ULN.

* Reference Figure 9, page 101 of the STF report

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ISS, integrated summary of safety; OTE, oteseconazole; PLB, placebo; TB, total bilirubin; ULN, upper limit of normal.

Table 50. Patients Identified With a Case of Temple’s Corollary, Safety Population, Trials 017, 012, 011 and 006 (ISS)

Patient ID	Age	Race	Arm	Max ALT_AST (xULN)	Max Bilirubin (xULN)
VMT-VT-1161-CL-011 (b) (6)	46	White	Placebo VMT-VT-1161-CL-011	4.7	0.5
VMT-VT-1161-CL-011 (b) (6)	35	White	Oteseconazole VMT-VT-1161-CL-011	3.55	0.58
VMT-VT-1161-CL-011 (b) (6)	31	White	Placebo VMT-VT-1161-CL-011	3.16	0.33
VMT-VT-1161-CL-011 (b) (6)	38	Asian	Oteseconazole VMT-VT-1161-CL-011	3.1	0.67
VMT-VT-1161-CL-011 (b) (6)	43	White	Oteseconazole VMT-VT-1161-CL-011	3.19	0.58
VMT-VT-1161-CL-011 (b) (6)	50	Black	Oteseconazole VMT-VT-1161-CL-011	4.58	0.83
VMT-VT-1161-CL-012 (b) (6)	52	White	Oteseconazole VMT-VT-1161-CL-012	5.97	0.42
VMT-VT-1161-CL-017 (b) (6)	36	White	Oteseconazole VMT-VT-1161-CL-017	9.16	0.83
VMT-VT-1161-CL-017 (b) (6)	21	White	Oteseconazole VMT-VT-1161-CL-017	5.58	0.67
VMTVT1161CL006 (b) (6)	58	White	Placebo VMTVT1161CL006	3.09	0.42
VMTVT1161CL006 (b) (6)	26	White	Oteseconazole VMTVT1161CL006	15.15	0.83
VMTVT1161CL006 (b) (6)	27	Asian	Oteseconazole VMTVT1161CL006	5.26	0.83
VMTVT1161CL006 (b) (6)	26	White	Oteseconazole VMTVT1161CL006	7.94	0.42

Source: datasets adsl.xpt, Software: R

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ID, identification; Max, maximum; ULN, Upper Limit of Normal

For narratives of all subjects in the oteseconazole arm with elevated liver transaminases, the reader is referred to Section [17.3.1](#) of the Appendix.

QT-Prolongation

Azole class drugs (e.g., fluconazole, voriconazole, and posaconazole) have been causally associated with QT prolongation, torsades de pointes and/or arrhythmias.

The table [below](#) summarizes the change in maximal post-baseline QTcF values among all participants with available baseline and postbaseline EKGs to identify any subjects with oteseconazole induced QTcF interval prolongations of >480 msec - ≤500 msec and >500 msec.

Table 51. QTcF Interval (msec) Shifts From Baseline for Graded Maximal Post-Baseline Toxicities, Safety Population, Trials 011, 012, 017 (ISS)

Laboratory Parameter	Baseline Toxicity Grade	Maximal Post-Baseline Toxicity Grade	Pooled OTE Phase 3 N=580 [n/N (%)]	Pooled PLB Phase 3 N=291 [n/N (%)]
QTcF Interval (msec), High	≤450 msec	≤ 450 msec	559/568 (98.4)	278/280 (99.3)
		>450 msec to ≤480 msec	9/568 (1.6)	2/280 (0.7)
	>450 msec to ≤480 msec	>450 msec to ≤ 480 msec	9/9 (100)	8/8 (100)
	>480 msec to ≤500 msec	0 (0.0)	0 (0.0)	0 (0.0)
	>500 msec	0 (0.0)	0 (0.0)	0 (0.0)
	Missing	≤ 450 msec	1/1 (100)	2/2 (100)

Source: adeg.xpt; Software: JMP and confirmed with R
Duration is approximately 50 weeks.

Subjects are counted only once within each group.

Abbreviations: ISS, integrated summary of safety; LLN, lower limit of normal; Ns, the total number of patients with baseline lab data available for each baseline toxicity subgroup and was assigned to that specific treatment group; n, the number of patients who meet the specific criteria; ULN, upper limit of normal; OTE, oteseconazole; PLB, placebo

A second table illustrating absolute changes from baseline of ≥ 30 -msec - < 60 msec and ≥ 60 -msec is found below.

Table 52. Percentage of Patients With Maximum Post-Baseline Absolute Change From Baseline QTcF Interval (msec), Safety Population, Trials 011, 012, 017 (ISS)

Laboratory Parameter	Absolute Change from Baseline	Pooled OTE Phase 3 N=580 n (%)	Pooled PLB Phase 3 N=291 n (%)
QTcF Interval (msec), High	>0 msec to <30 msec	392 (67.6)	210 (72.2)
	≥ 30 to <60 msec	18 (3.1)	6 (2.1)
	≥ 60 msec	0 (0.0)	0 (0.0)
	Missing	156 (26.9)	64 (22)

Source: adeg.xpt; Software: JMP and confirmed with R
Duration is approximately 50 weeks.

Subjects are counted only once within each group.

Abbreviations: ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients who meet the specific criteria; OTE, oteseconazole; PLB, placebo

Clinical Reviewer's Comment: *The clinical reviewer identified no increases in the QTcF interval to suggest the potential for oteseconazole induced QTcF interval prolongations of >500 msec, particularly among participants with baseline QTcF intervals ≤ 450 msec. There were no participants with a baseline QTcF interval of >480 msec or >500 msec. No subjects developed QTcF interval increases of >480 msec to ≤ 500 msec or QTcF interval increases of >500 msec while on oteseconazole or placebo.*

In addition, the reviewer conducted an analysis of the absolute change in baseline and post-baseline QTcF intervals. The reviewer found that most participants had an absolute post-baseline QTcF interval change of <30 msec when compared to their baseline QTcF value. Eighteen (3.1%) and 6 (2.1%) participants in the oteseconazole and placebo arms, respectively, developed an absolute post-baseline change of ≥ 30 msec to <60 msec from their baseline QTcF interval. Importantly, there were no subjects observed to have an absolute post-baseline QTcF interval increase of ≥ 60 msec. It is noted that there was no comparator positive control drug. Since the placebo comparator drug was not a positive control, no definitive statement could be

made on whether oteseconazole was not associated with QTcF interval prolongations based on the phase 3 trials. Nevertheless, in the context of the phase 3 trials, no QTcF prolongations were observed.

The clinical reviewer performed CMQs and SMQs to search for any PTs suggestive of QTc prolongations (e.g., ventricular arrhythmias, torsades de pointes, cardiac arrest, sudden death) in the phase 3 (Trials CL-011, CL-012, and CL-017) and the phase 2b (Trial CL-006) trials and found none. The search only yielded such PTs as: atrial fibrillation (1 subject), bradycardia, palpitation, syncope (1 subject), and tachycardia among participants in the oteseconazole arm. There were no noted differences between the oteseconazole and placebo arms.

Drug Allergy/Hypersensitivity/Anaphylactic Reactions

The reviewer identified several PTs potentially suggestive of hypersensitivity reactions in the phase 3 integrated summary of safety (ISS) database. These PTs included: blister (reported term: vesicles on trunk), dermatitis; dermatitis allergic; dermatitis contact; drug eruption; drug hypersensitivity; mouth ulceration; rash generalized; swelling; swelling face; and urticaria. There was a total of 27 TEAEs, none of which were SAEs, that were reported in a total of 21 subjects: 15 (2.6%; 15/580) subjects in the oteseconazole arm (with 21 TEAEs) and 6 (2.1%; 6/291) in placebo subjects (6 TEAEs). A single case of dermatitis occurred pre-treatment in a subject in the oteseconazole arm. No cases of anaphylaxis were reported among oteseconazole-exposed subjects. Narratives for these subjects can be found in Section [17.3.3](#) of the Appendix.

Other Adverse Events of Special Interest

Outside of the above-described adverse events of special interest (AESI), the clinical reviewer performed Medical Dictionary for Regulatory Activities -based Adverse Event Diagnostics CMQ and SMQ searches of the phase 3 trials (Trials CL-011, CL-012, and CL-017) and of the supportive phase 2b trial (Trial CL-006) to identify several AESI that have been associated with at least one or more azole-class drugs including: (a) adrenal dysfunction, (b) pancreatitis, (c) phototoxicity, (d) renal impairment, (e) seizure, and (f) visual disturbances.

Neither the CMQs nor SMQs yielded any safety signals for potential cases of adrenal dysfunction, anaphylaxis, renal impairment, phototoxicity, seizures, and/or visual disturbances. A single subject in the oteseconazole arm of Trial CL-006, Subject (b) (6) had two treatment-emergent SAEs, one of which was an SAE resulting in withdrawal of oteseconazole and coded to the PT pancreatitis (Study Days 25 – 33). The event was deemed unrelated to oteseconazole exposure and occurred in a participant with a known history of chronic pancreatitis. This subject was discussed in greater detail under Section [7.6.7.1](#) Serious Adverse Events for Trial CL-006, and the narrative can be found in Section [17.3](#) of the Appendix.

7.6.7.2. Summary of Safety Findings From Other Studies

Overall Adverse Event Summary, Nonpivotal Phase 1 and 2 Trials (Trial CL-004 and Trial CL-005)

Phase 2a Study CL-004 (Acute VVC)

The Applicant conducted a small phase 2a multi-center, randomized, double-blind, active-controlled, parallel-group proof of concept trial evaluating three separate oteseconazole dosing regimens: 300 mg daily x 3 days (900 mg total); 600 mg daily x 3 days (1800 mg total); and 600 mg twice daily x 3 days (3600 mg) all compared to single-dose fluconazole in the treatment of patients with moderate to severe acute VVC. The safety population was comprised of 55 subjects, each randomized to one treatment arm: a total of 14 subjects were randomized to the 900 mg arm (300 mg daily); 12 subjects were randomized to the 1800 mg arm (600 mg daily); 14 subjects were randomized to the 3600 mg arm (600 mg twice daily); and 15 were randomized to the active control single-dose fluconazole.

A total of 62 treatment-emergent adverse events (TEAEs) occurred among 55 subjects, with the fluconazole arm having the greatest number of TEAEs (22), followed by the oteseconazole 900 mg group (19 TEAEs); the 1800 mg group (17 TEAEs) and the 3600 mg group (4 TEAEs). There were no treatment-emergent SAEs that occurred in any treatment arm during this trial. There were no subjects with CPK elevations in the oteseconazole arm.

The most common TEAEs across all oteseconazole arms were: PT: nasopharyngitis (5 TEAEs, 5 subjects) (pooled PT: upper respiratory tract infection, nasopharyngitis, oropharyngeal pain [reported term: sore throat] and pharyngitis); followed by bacterial vaginosis (3 TEAEs, 3 subjects) and nausea (3 TEAEs, in 2 subjects). The majority of TEAEs in the placebo arm were reported under the Infections and infestations SOC (11 TEAEs, 6 subjects), with the most commonly cited TEAEs being: bacterial vaginosis (2 TEAEs, 2 subjects), nasopharyngitis (2 TEAEs, 2 subjects), and Pregnancy (2 TEAEs, 2 subjects) under the Pregnancy, puerperium, and perinatal conditions SOC.

Most TEAEs in the oteseconazole 900 mg arm occurred under the Infections and infestations SOC (9 TEAEs), followed by the Skin and subcutaneous tissue disorders SOC (3 TEAEs). BV and nausea were the most commonly reported TEAEs (2 TEAEs); however, the latter PT occurred in the same subject and was deemed to be related to the study drug by the Investigator. The 2 cases of BV were not deemed to be related to oteseconazole. AESIs included the PTs dermatitis contact (Study Day 8-29) which was deemed unrelated to oteseconazole by the Study Investigator and the PT urticaria (2 TEAEs) which occurred in the same patient (Study Days 8-35 and 35-41), with the first occurrence deemed related to oteseconazole. The Study Investigator assessed a single TEAE coded to the PT dyspareunia (Study Days 26-30) as being related to the drug. All but one TEAE resolved, many required new therapeutic treatments, and none had a severity intensity of greater than 2.

The majority of TEAEs in the oteseconazole 1800 mg cohort occurred in the Nervous system disorder SOC (5 TEAEs), followed by the Gastrointestinal disorders SOC and the Infections and infestations arm (3 TEAEs each) SOC. Nausea (3 events) and dizziness (2 events) were the most frequently reported TEAEs; however, four of these five events occurred in the same subjects. All were self-limited and were believed to be related to the drug. Otherwise, there was one case each

of bacterial vaginosis; headache, dysgeusia, and vulvovaginal pruritus that were deemed by the Study Investigator to be related to the study drug. In addition, and based on the presumed oteseconazole safety profile, there was a single TEAE of UTI that was deemed to be unrelated to oteseconazole exposure. Notably, there was a single subject with a PT coded to “Liver function test increased” (Study Day 18 to 32) that was deemed as unrelated to study drug. Most all events were self-limited. Several subjects, including those with BV and UTIs, required a new treatment.

As stated earlier, there were a total of 4 TEAEs reported in the 3600 mg oteseconazole arm: two occurring in the same subject under the Reproductive system and breast disorders SOC (PTs: vulvovaginal pruritus and vulvovaginal erythema), and one each occurring in the Infections and infestations SOC (PT: pharyngitis) and Gastrointestinal disorders SOC (PT: abdominal pain). None of the reported events were assessed as being related to the study arm and three were reported to have resolved.

Phase 2b Trial CL-005 (Onychomycosis)

The Applicant conducted a 259 participant (ITT Population) dose ranging trial evaluating oteseconazole safety, tolerability, efficacy, and PK study in males and females with onychomycosis. Trial CL-005 was a multi-center, randomized, double-blind, active-controlled, parallel-group trial. The safety findings in Trial CL-005 were similar to the safety findings in the oteseconazole arms in the phase 3 trials and the supportive phase 2 trial CL-006, namely nasopharyngitis; sinusitis, and nausea.

The Safety Population consisted of 212 persons randomized into four oteseconazole treatment arms: 53 subjects were randomized into the oteseconazole 4200 LD/300 mg 10 weeks arm; 53 subjects were randomized into the oteseconazole 4200 LD/300 mg 22 weeks arm; 52 subjects were randomized into the oteseconazole 8400 LD/600 mg 10 weeks arm; 54 subjects were randomized into the oteseconazole 8400 LD/600 mg 22 weeks arm, and 47 subjects were randomized into the placebo arm. Overall, there were a total of 471 adverse events (AEs) occurring in: 122 of 212 (57.6%) oteseconazole subjects (across all oteseconazole arms) with 395 TEAEs and 27 of 47 subjects (57.5%) in the placebo arm who experienced a total of 76 TEAEs.

Across all oteseconazole treatment arms, the majority of all TEAEs occurred in the Infections and infestations SOC (76 TEAEs); followed by the Gastrointestinal disorders SOC (57 TEAEs); the Injury, poisoning and procedural complications SOC (50 TEAEs); Musculoskeletal and connective tissue disorders SOC (42 TEAEs); and the Skin and subcutaneous tissue disorders SOC (36 TEAEs). There was a total of 14 SAEs that occurred in 9 subjects across all oteseconazole treatment arms, including three subjects with multiple SAEs (Subject (b) (6) PT: osteoarthritis x 2; Subject (b) (6) PT: hemorrhagic anemia, acute kidney injury, pyrexia, multiple fractures; and Subject (b) (6) PTs: pulmonary embolism and artery dissection). The most frequent TEAEs occurring across oteseconazole treatment arms were: nasopharyngitis (15.1%) (32 of 212 subjects) (pooled PTs: upper respiratory tract infection [18 subjects]; nasopharyngitis [13 subjects]; oropharyngeal pain [1 subject]; and pharyngitis streptococcal [1 subject]); ingrowing nail (6.1%) (13 of 212 subjects); sinusitis (5.2%) (11 of 212 subjects) (pooled PTs: sinusitis [11 subjects], acute sinusitis [1 subject]) and nausea (4.7%) (10 of 212 subjects).

There was a single subject, (Subject CL-005 (b) (6)), in the oteseconazole 4200 mg/300 mg x 10 weeks arm with a reported, self-limited Grade 1, on-treatment, non-SAE, TEAE with a PT coded to “Blood creatine phosphokinase increased” (Study Days 29 to 35). The final day of oteseconazole exposure in this subject was Study Day 85. The event reportedly required no change in oteseconazole dosing and was determined by the Study Investigator to be unrelated to oteseconazole.

Allergic/hypersensitivity reactions, an AESI, were reported across all four oteseconazole arms (PTs: dermatitis [2 TEAEs, in 2 subjects]), dermatitis allergic, dermatitis atopic, dermatitis contact (5 TEAEs, in 2 subjects), and hypersensitivity (reported term: allergic reaction, occurred post oteseconazole treatment, Study Days 318-329).

The SOC with the most TEAEs in the placebo arm was the Infections and infestations SOC (21 TEAEs), followed by the Gastrointestinal disorders SOC (12 TEAEs), and the Musculoskeletal and connective tissue disorders SOC (6 TEAEs). The most common TEAE in the placebo arm was nasopharyngitis (pooled PTs: upper respiratory tract infection and nasopharyngitis) (13 TEAEs, 7 subjects).

Phase 1 Studies

The Applicant conducted a total of eight phase 1 trials in healthy, adult subjects, including five trials that were included in the Applicant’s ISS data set (201 subjects in ISS: 177 in the oteseconazole arm and 24 in the placebo arm). These trials were:

- CL-001, a first-in-human single dose escalation trial; (n=23 subjects, 33 AEs)
- CL-002, a multiple dose escalation; (n=12 subjects, 20 AEs)
- CL-008, an ethno bridging trial; (n=17 subjects, 35 AEs)
- CL-013, a food effect trial; (n=17 subjects, 45 AEs)
- CL-016, an absorption, distribution, metabolism, excretion trial; (n=9 subjects, 37 AEs)

Of the five phase 1 trials included in the Applicant’s ISS data set, 78 subjects had a total of 170 AEs. Seventy-six of these subjects had the 162 observed TEAEs discussed below: 66 in the oteseconazole arm (with a total of 147 TEAEs) and 10 subjects in the placebo arm (with a total of 15 TEAEs). The oteseconazole doses studied in these Phase 1 studies were: 5 mg (4 subjects); 10 mg (3 subjects); 20 mg (3 subjects); 40 mg (5 subjects); 80 mg (4 subjects); 150 mg (16 subjects); 160 mg (1 subject); 300 mg (6 subjects); 320 mg (5 subjects) and 600 mg (19 subjects).

The SOCs with 10 or more reported TEAEs in the oteseconazole arm, in descending order were: the Nervous system disorders SOC (35 TEAEs); the Gastrointestinal disorders SOC (27 TEAEs); the Musculoskeletal and connective tissue disorders SOC (23 TEAEs); the General disorders and administration site conditions SOC (18 TEAEs); and the Injury, poisoning and procedural complications and Skin and subcutaneous tissue disorders SOCs (10 TEAEs each). The most commonly occurring TEAEs among oteseconazole participants were reported under the following PTs: headache (25 TEAEs; in 17 participants); nausea (8 TEAEs; in 8 participants); constipation (7 TEAEs; in 6 participants); back pain and myalgia (6 TEAEs; in 6 participants).

Notably, 4 subjects in the oteseconazole phase 1 trials had TEAEs coded to the PT: blood creatine phosphokinase elevated. These occurred in four subjects receiving four different oteseconazole doses: 5-mg (Study Days 4-16), 10-mg (Study Days 24-73), 40-mg (Study Day 35

to 41), and 320-mg (Study Days 49 to 51). The subjects who received oteseconazole 5 mg and 10-mg were in the single dose study and the subjects who received 40 mg and 320-mg doses were in the 7-day multiple dose escalation study. The reported CPK elevations had an onset of Study Day 4 through Study Day 49 relative to the start of oteseconazole exposure treatment. Three of the four participants were reported to have recovered from the event, with a single event with an outcome reported as unknown. None of these reported events were SAEs and none were deemed to be related to the study drug by the Study Investigator. Actions take with study drug were reported as unknown for the two subjects in the multiple ascending dose study and not applicable for the two subjects in the single dose study.

There were six subjects in the oteseconazole arm who were reported as having myalgia, one of whom, Subject (b) (6) (PT: myalgia, Study Days 7-11), was also reported to have had elevated CPK levels (Study Day 4-16). A single subject in the oteseconazole arm (Subject (b) (6) (b) (6) 10-mg) was reported to have had a TEAE coded to ALT increased (Study Day 7-14), which was self-limited and deemed by the Study Investigator to be related to the study drug. This subject was also observed to have CPK elevations (Study Days 24-73), although these events did not occur concurrently and therefore were likely unrelated. There were no PTs suggestive of QT prolongation.

There was a total of 15 TEAEs that occurred among 10 subjects in the phase 1 study placebo arm. The SOCs with the most TEAEs in this arm, were, in descending order: the Musculoskeletal and connective tissue disorders SOC (4 TEAEs); the Investigations SOC (3TEAEs); and the Nervous system disorders SOC and Skin and subcutaneous tissue disorders SOC (with 2 TEAEs each). The most common TEAE in the placebo arm was the PT: back pain (2 subjects), with all other PTs reported in one subject each. Notable TEAEs in the placebo arm were coded to the PTs: arthralgia, ALT increased, and blood creatine phosphokinase (with each of these PTs occurring in one subject).

7.6.7.3. 120 Day Safety Update

In their 120-Day Safety Report, the Applicant provided pregnancy updates from completed phase 3 Trials CL-012 and CL-017; as well as safety data from their completed thorough QT (TQT) study (Trial CL-018); their ongoing hepatic and renal studies (Trial CL-019 and CL-020, respectively); and additional safety data on several ongoing studies conducted outside of the United States. According to the Applicant no new oteseconazole safety signals were identified based on the reported data.

Phase 1 Thorough QT (TQT) Study (CL-018)

The Applicant reported that there were no clinically relevant effects on heart rate (HR) or cardiac conduction (the PR and QRS intervals) among the 29 oteseconazole exposed subjects (oteseconazole 600 mg daily administered on Days 1 to 13, and a single dose of 1200 mg administered on Day 14). Of the 141 TEAEs that occurred in the study, none were determined to be severe. The most frequent ($\geq 7\%$) on-treatment TEAEs (Days 1 to 13) were headache, fatigue, nausea, and constipation; and the most frequent post-treatment TEAEs (Days 14+) were headache, dizziness, nausea, and constipation. There were no reported deaths or SAEs.

Hepatic and Renal Impairment

No deaths, SAEs, discontinuations, or any significant findings were reported in the ongoing hepatic (Trial CL-019) or renal (Trial CL-020) impairment studies.

Pregnancy Updates

There were three pregnancies updated, two from Trial CL-012 and one from Trial CL-017, that included two live, healthy births (including one premature birth at 32-weeks), and one elective abortion.

Ongoing Clinical Studies

The Applicant reported that the three studies conducted in support of the foreign marketing applications yielded no new oteseconazole-related safety signals. According to the Applicant, there were no reported deaths, nonfatal SAEs, TEAEs resulting in discontinuations, or any other reported significant findings.

For further details on the Applicant's thorough QT (TQT) study (Trial CL-018) and hepatic and renal studies (Trials CL-019 and CL-020, respectively), please refer to Section [8.1](#) of this review.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Nonclinical Ocular Findings and Implications for Labeling

Issue

Ocular abnormalities were observed in rat pups born to dams dosed with oteseconazole while pregnant in four separate pre- and postnatal toxicity studies. Ocular abnormalities included cataracts/opacities, sometimes accompanied by exophthalmos, buphthalmos, optic nerve/retinal atrophy, lens degeneration and hemorrhage and were observed in the offspring of rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day, (about 3.5 times the recommended human dose based on area under the concentration-time curve [AUC] comparisons). Details of these studies are included in Section III: Appendix Pharmacology Toxicology: Additional Information and Assessment.

Background

The Applicant is proposing to market VIVJOA to reduce the incidence of recurrent vulvovaginal candidiasis, a condition common among females of reproductive potential. These ocular findings may indicate a risk of cataracts, opacities and other ocular findings in the children of patients who are pregnant when the drug is present in the plasma. The prolonged drug exposure window of approximately 690 days (based on 5 times the half-life) of oteseconazole makes it very difficult to adequately mitigate these potential risks.

Assessment

[Table 53](#) shows the increased incidences of ocular abnormalities in Study 1234003 in rat pups born to mothers dosed with oteseconazole via oral gavage once daily from Gestation Day 6 through Lactation Day 20. Similar increases in ocular abnormalities were also observed in Studies 1234001, 1234002 and 1234004.

Table 53. Number of Animals With Specific Ophthalmology Findings on Postnatal Day 21 in Rat Pups Born to Mothers Dosed With Oteseconazole via Oral Gavage Once Daily From Gestation Day 6 Through Lactation Day 20

Findings	0 mg/kg N=144	7.5 mg/kg N=132
Cataract	6	31
Hyphema	1	19
Corneal ulceration	0	4
Corneal perforation	1	2
Buphthalmos	0	3
Iridial hemorrhage	0	1

Source: Reviewer generated data based on data from Study #1234003

These findings will be described in the physician's prescribing information.

Conclusion

Based on findings of ocular abnormalities in several pre-clinical studies, coupled with oteseconazole's prolonged drug exposure window of approximately 690 days in humans (which would preclude reasonable use of birth control), the review team concluded that the administration of oteseconazole in females of childbearing potential should be contraindicated.

7.7.2. CPK Elevations

Issue

- Transient, largely asymptomatic, unexplained elevations in CPK of up to ≥ 10 x ULN (Grade 3) and ≥ 20 x ULN (Grade 4) were observed without evidence of acute kidney injury. The DAIDS toxicity grading scale was used to evaluate CPK elevations. See also Section [7.6.6.](#), Laboratory Findings, and [Table 44](#).
- Most CPK elevations were accompanied by mild elevations of AST and/or ALT.
- Subject narratives describing each event are found in Section [17.4](#) of the review.

Background

When using the DAIDS toxicity grading scale, an imbalance in the frequency of Grade 3 and Grade 4 CPK elevations was detected between the oteseconazole and placebo arms in the combined phase 3 trials (11 of 569; 1.9% versus 2 of 275, 0.7%) and in the supportive phase 2b trial (Trial CL-006) (6 of 160; 3.8% versus 0 of 45; 0.0%). It is noted that a 2:1 randomization ratio was used in the phase 3 trials (CL-011, CL-012, and CL-017); whereas a 1:1:1:1 randomization scheme was used for the phase 2b trial (4 dosing cohorts received oteseconazole and a single cohort received placebo).

Assessment

Using the DAIDS toxicity grading scale, CPK elevations as high as ≥ 20 x ULN were observed either during treatment with oteseconazole, within one-month post-oteseconazole exposure, between 2-4 months postexposure, and in some instances 5-8 months post-oteseconazole exposure. When observing subject level CPK data it is challenging to clearly implicate oteseconazole as being a contributor to this safety finding; however, when looking at the data in aggregate it appeared that elevations out to 4 months post treatment were not unlikely given oteseconazole's half-life of 114-138 days (3.8 months). In most cases, the observed CPK elevations co-occurred with Grade 1 to 4 AST elevations, which varied based on the amplitude of the CPK elevation. ALT elevations were also observed with increased CPK levels, but increases in ALT levels did not occur as consistently with CPK elevations as increases in AST. This is most likely because AST is found in skeletal muscle whereas ALT is more specific to the liver. Even in the setting of Grade 4 CPK elevations, there was no evidence of resultant acute kidney injury associated with the CPK elevations.

An information request (IR) was sent to the Applicant on September 24, 2021, requesting any collateral information, including whether affected participants engaged in strenuous exercise, drug and alcohol use (exclusions), or exhibited baseline electrolytes disorders (e.g., hypokalemia, hypophosphatemia, or hypocalcemia) that could explain these elevations. The reviewer could not identify any patients with the observed elevations who were taking lipid lowering medications such as statins or fibrates.

In most instances, the Applicant did not consider these elevations to be causally linked to oteseconazole administration given the transience and temporality of the findings. However, they were unable to provide alternate explanations for the observed findings.

It should be noted that most CPK elevations in the subject narratives discussed in Section [17.4](#) of the Appendix were not identified by either the Study Investigator or the Applicant as TEAEs, but rather were independently identified by the clinical reviewer in search of post-baseline maximal CPK values that were at or around ≥ 1000 U/L. CPK elevations have been documented, in the postmarket setting, in otherazole-class drugs, including: itraconazole which has been associated with "blood creatine phosphokinase increased." In addition, "creatin phosphokinase increased" has been identified as a less common adverse reaction associated with voriconazole (under the Metabolic and Nutrition SOC).

In a December 7, 2021, reply to a clinical and clinical pharmacology IR, the Applicant attributed the observed CPK imbalances to the differences in randomization scheme employed in the clinical trials. The Applicant indicated that risk factors most frequently associated with CPK elevations (e.g., trauma, seizure, medications, limb compression, electrolytes disorders, and viral infections) had not been identified in most subjects with these elevations. However, the Applicant acknowledged that for all subjects with witnessed CPK elevations, they could not confirm whether subjects engaged in strenuous exercise or substance abuse (e.g., alcohol, cocaine, methamphetamine). It is noted, however, that alcohol and drug use were exclusions for study participation.

As part of the IR, the Applicant conducted an exposure-response analysis in order to investigate the potential association between oteseconazole exposure and the occurrence of a Grade 3/4 CPK elevation, or between oteseconazole exposure and the time to first occurrence of a Grade 3/4 CPK elevation. The Applicant's analysis used quartiles of maximum plasma concentration (C_{max})

at the time of a Grade 3/4 CPK elevation or at any time for subjects without CPK elevation as an exposure metric for oteseconazole, and included the placebo/fluconazole arm as a comparator bin (null exposure). The Applicant's analysis did not identify a positive relationship either between oteseconazole concentrations and Grade 3/4 CPK elevations or between oteseconazole concentration and the time to first occurrence of the Grade 3/4 CPK elevation. The reviewer's evaluation used different quantiles of either C_{max} or average oteseconazole concentrations (C_{avg}), as oteseconazole exposure metrics. The reviewer did not identify a consistent trend or a statistically significant relationship either between the oteseconazole exposure and the occurrence of Grade 3/4 CPK elevations or between the oteseconazole exposures in patients with CPK elevation and the time to first occurrence of CPK elevation. In conclusion, under the studied and the proposed dosage for RVVC, there is no clear evidence of an association between the extent of oteseconazole exposure and the occurrence of CPK elevations (most of which were transient in nature).

Conclusion

The observed CPK elevations will be described under sub-section 6.1 Clinical Trial Experience of the VIVJOA label. CPK elevations have also been noted in the US prescribing information for the azole antifungals itraconazole and voriconazole, but not in the fluconazole or posaconazole US prescribing information. With the exception of one subject, Subject (b) (6) in Trial CL-017 who developed a Grade 4 CPK elevation of 14833 U/L (77.3 x ULN) and a concomitant TEAE of myalgia, most subjects with CPK elevations were otherwise asymptomatic.

8. Therapeutic Individualization Therapeutic Individualization

8.1. Intrinsic Factors

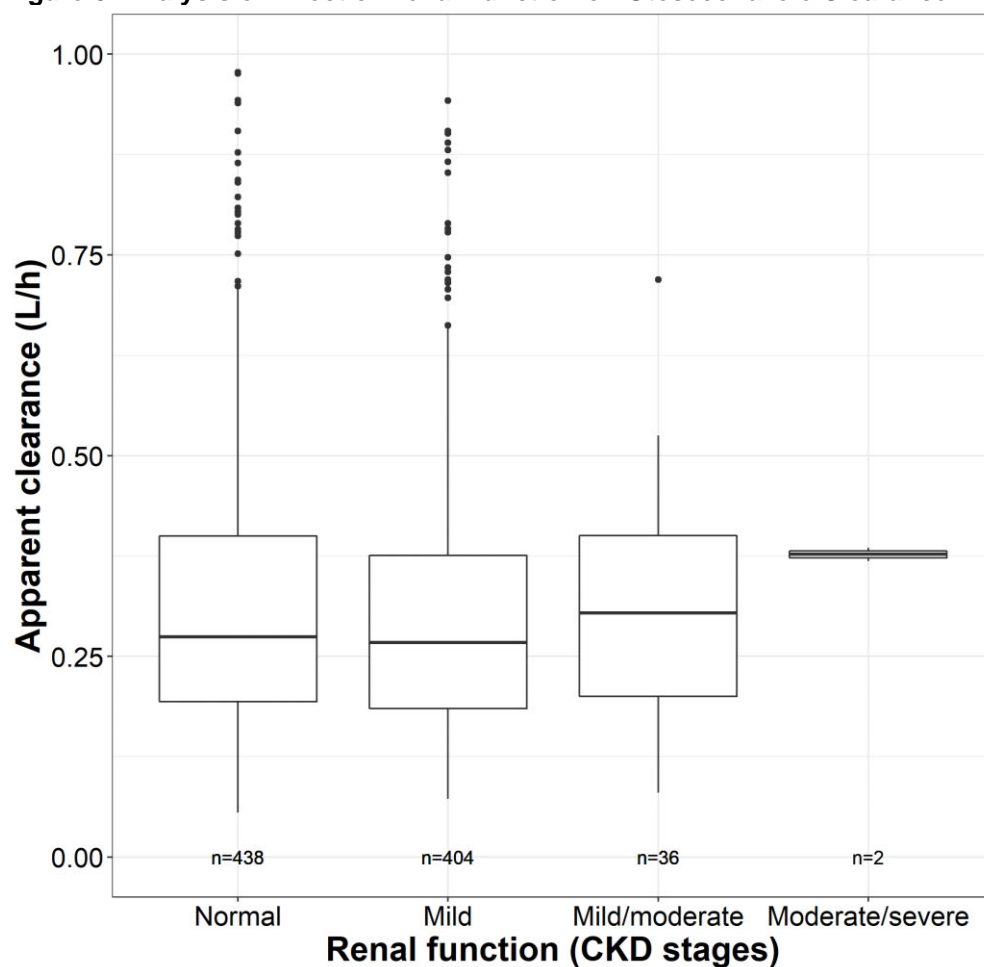
Hepatic Impairment

The effect of hepatic impairment on the PK of oteseconazole was not studied. In vitro, oteseconazole was not metabolized in incubations with pooled human liver microsomes, and no metabolites were identified in the human mass balance study. Results of the mass balance study showed that out of 82% of administered radioactivity that was recovered, 56% was in feces. Because of the prolonged fecal recovery of radiolabeled oteseconazole, biliary excretion appears to be the primary elimination pathway for oteseconazole (accounting for the excretion of an estimated 66% of the absorbed dose); therefore, hepatic impairment may impact the elimination of oteseconazole. Based on the lack of significant hepatic metabolism, and the acceptable safety profile of oteseconazole in patients with RVVC at 2-fold higher doses (see Section 7.6.1) than the recommended dose, mild hepatic impairment (Child-Pugh A) is not expected to have a clinically meaningful impact on the PK of oteseconazole. However, there is insufficient information to predict the effect of moderate or severe hepatic impairment on the PK of oteseconazole. Therefore, in patients with moderate to severe hepatic impairment (Child-Pugh B-C), use of oteseconazole is not recommended due to the possible risk of significant drug accumulation.

Renal Impairment

A dedicated renal impairment study was not conducted. Results of the human mass balance study showed that out of 82% of administered radioactivity that was recovered, 26% was in urine. In population PK analysis, mild to moderate renal impairment (based on estimated glomerular filtration rate calculated using the modification of diet in renal disease [MDRD] equation) was not identified as a significant covariate for oteseconazole clearance as shown in [Figure 6](#). Based on this analysis, the proposed dose is expected to be safe in patients with mild to moderate renal impairment. Population PK analysis of the impact of severe renal impairment on CL was less informative because only 2 subjects were identified under this renal function category. Furthermore, oteseconazole has not been studied in subjects with ESRD. Because experience is limited in these populations, use of oteseconazole is not recommended in patients with severe renal impairment or ESRD.

Figure 6. Analysis of Effect of Renal Function on Oteseconazole Clearance



Source: Reviewer analysis
Abbreviations: CKD, chronic kidney disease.

Other Intrinsic Factors

Population PK analysis indicated that sex, race and age (within adults) do not have a clinically significant effect on the PK of oteseconazole. In subjects weighing <40 kg, population PK

predicted AUC is up to 2-fold higher than the AUC in subjects with body weight 60 – 70 kg (See Section 14.3). Because only 1 subject weighing <40 kg (with actual weight 36 kg) was identified across phase 3 clinical studies, the clinical significance of this observation is unknown. Notably, subjects enrolled in phase 3 trials weighing 40 to 59 kg did not appear to have increased TEAEs compared to those weighing at least 60 kg. Therefore, based on the available information, no dosage adjustment is needed based on body weight.

8.2. Extrinsic Factors

8.2.1. Food Effect

The review team recommends that oteseconazole be administered with food based on the following available information:

- (1) The dedicated food effect study (Study VMT-VT-1161-CL-013) evaluated the impact of high-fat, high-calorie (900-1000 kcal with 500-600 kcal from fat) and low-fat, low-calorie (650 kcal with 117 kcal from fat) meals on the PK of oteseconazole following administration of the to-be-marketed capsule formulation. Oteseconazole AUC increased by 36% with a high-fat meal but was unimpacted by a low-fat meal. Given the lack of an Exposure-Response for oteseconazole, the clinical relevance of the 36% increase in exposure with high fat, high calorie food cannot be ascertained. Nonetheless, administering oteseconazole with food (particularly, high fat food) could confer therapeutic benefit.
- (2) In the food effect study, the incidence of AEs was higher in the fasted state and with a low-fat meal, (i.e., 50%, N=12/cohort) compared to administration of oteseconazole with a high-fat meal (i.e., 17%, N=12).
- (3) In Phase 3 trials, patients were instructed to take oteseconazole with their largest meal of the day. Patients in the Phase 2 RVVC trial were simply instructed to take oteseconazole with food. Although neither the caloric contents nor types of food consumed were recorded for these trials, ultimately, the efficacy of oteseconazole in these studies was evaluated under fed conditions.

8.2.2. Drug Interactions

It is unlikely that oteseconazole PK is affected by concomitant medications because oteseconazole does not undergo metabolism and is not a substrate of major transporters, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, OAT1, and OAT3.

It is unlikely that oteseconazole would impact the PK of the concomitant medications, except for BCRP substrates. The review team recommended that “Concomitant use of oteseconazole may increase the exposure of drugs that are BCRP substrates (e.g., rosuvastatin), which may increase the risk of adverse reactions associated with these drugs. Use the lowest possible starting dose or consider reducing the dose of these drugs and monitor for adverse reactions.”

The Applicant did not conduct in vitro studies to evaluate whether oteseconazole is a substrate or an inhibitor of the multidrug and toxic compound extrusion (MATE) transporters which are expressed on the apical side of the kidney tubules (i.e., MATE1 and MATE2-K) and bile canaliculi (i.e., MATE1), where they mediate renal tubular secretion and biliary secretion,

respectively. The Applicant asserted that based on overlapping substrate specificity between OCTs and MATE, and oteseconazole's physicochemical properties (i.e., high molecular weight, neutral charge, high protein binding and low aqueous solubility), oteseconazole is unlikely to be a MATE substrate. However, there is insufficient evidence to support this assertion. Where the potential role of MATE in the urinary excretion of oteseconazole is concerned, human mass balance study results indicated that 26% of radiolabeled oteseconazole was recovered in urine. However, the fraction of parent drug subject to active renal secretion is unknown. Nonetheless, because the mass balance study results suggest biliary excretion as the primary elimination pathway for oteseconazole, the contribution of MATE1 transporter to the biliary excretion of oteseconazole cannot be ruled out.

The Applicant further indicated that the lack of significant inhibitory activity for OCT2 in vitro suggested that oteseconazole is unlikely to inhibit MATE. Although MATE inhibitors often overlap with OCT2 inhibitors, there are exceptions such as GAVRETOTM (pralsetinib), which inhibits MATE1 and MATE2-K but does not inhibit OCT1/2. Given that the potential for oteseconazole drug interactions with MATE substrates and inhibitors cannot be discounted, the review team has recommended and obtained the Applicant's concurrence for a post marketing evaluation of oteseconazole as a substrate and inhibitor of MATEs (MATE1 and MATE2-K) in vitro.

Please see below for details of drug-drug interaction studies.

Effect of Other Drugs on Oteseconazole

Cytochrome P450 Inhibitors and Inducers

Oteseconazole may be co-administered with cytochrome (CYP) P450 isoenzyme inhibitors and inducers without dosage adjustment based on the observation that oteseconazole is stable in human liver microsomes in vitro.

Cell Membrane Transporter Inhibitors

Oteseconazole may be co-administered with inhibitors of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 without dosage adjustment based on in vitro study results.

Effects of Oteseconazole on Other Drugs

It is unlikely that oteseconazole would have impact on the PK of the concomitant medications that are the substrate of major CYP enzymes (i.e., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6), or that are the substrate of major cell membrane transporters (i.e., P-gp, OATP1B1, OATP1B3, OCT2, OAT1, and OAT3) because oteseconazole did not impact the metabolism of probe substrates for above mentioned CYP enzymes, or inhibit above mentioned cell membrane transporters at clinically relevant concentrations.

CYP3A4 Substrates

In clinical drug interaction study (VMT-VT-1161-CL-007), oteseconazole did not cause clinically significant inhibition of midazolam metabolism and caused weak induction of CYP3A4 based on around 36% decrease in AUC of midazolam. However, it is to be noted that the dosage regimen of oteseconazole used in this study was 600 mg once daily for 14

consecutive days, but the proposed maintenance dose is 150 mg weekly. Therefore, low to no induction is expected at the recommended dose. Also, no clinically significant differences in pharmacokinetics of oral contraceptives of ethinyl estradiol and norethindrone, CYP3A4 substrate, were observed when administered concomitantly with oteseconazole (see details below). Therefore, the review team accepted the Applicant's proposal that no dosage adjustment is needed when CYP3A4 substrates are co-administered with oteseconazole.

Substrates of P-gp and BCRP

Clinical drug interaction study (VMT-VT-1161-CL-015) showed that digoxin C_{max} and area under the curve from 0 to 24 hours (AUC_{0-24h}) were similar (differences in mean ratios were approximately 6-13%) upon coadministration of digoxin with oteseconazole. However, coadministration of a single dose of 150 mg oteseconazole increased rosuvastatin C_{max} , AUC_{0-24h} , and area under the curve from zero to infinity ($AUC_{0-\infty}$) approximately 84% to 87%; and coadministration of 150 mg oteseconazole for 14 days increased rosuvastatin C_{max} , AUC_{0-24h} and $AUC_{0-\infty}$ approximately 94% to 118%. The review team agrees with the Applicant that oteseconazole inhibits BCRP but does not inhibit P-gp. However, the review team disagrees with the Applicant's proposed labeling language, (b) (4)

(b) (4) Instead, based on the mitigation strategy recommended for approved drugs which also have drug interaction with rosuvastatin, increase rosuvastatin's systemic exposure at a similar level, and increased creatinine kinase in clinical studies, the review team recommends using the lowest possible starting dose or consider reducing the dose of drugs that are BCRP substrates and monitor for adverse reactions.

Combined Oral Contraceptive

When a combined oral contraceptive containing ethinyl estradiol (EE) and norethindrone (NE) was co-administered with oteseconazole in a clinical drug interaction study, EE C_{max} , AUC_{0-24h} , AUC_{0-t} , and $AUC_{0-\infty}$, were increased approximately 12% to 20% and NE C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, were similar (difference of 3% to 7%) compared to when administered alone. Therefore, no clinically meaningful effect of the concomitant use of oral contraceptives with oteseconazole would be anticipated, and thus no dosage adjustment is needed.

8.3. Plans for Pediatric Drug Development

The oteseconazole IND had an agreed initial pediatric study plan that contained plans to request a partial waiver in pediatric patients less than 12 years of age as well as all male patients and to enroll female patients 12 to less than 18 years of age. Eligibility criteria for the phase 3 trials included postmenarchal females ages 12 years old and above; however, only 3 adolescent subjects enrolled into the phase 3 trials. Based on the preclinical findings and the review team's decision to contraindicate the use of oteseconazole in females who are not of reproductive potential, studies in adolescents will be waived. This will be addressed in the appropriate sections of the oteseconazole US prescribing information.

Oteseconazole was presented to the Pediatric Review Committee on December 14, 2021. The PeRC agreed with the Division's recommendation to grant a full waiver for pediatric studies in the above-mentioned groups for the following reasons:

- Less than 12 years of age and males of all ages because studies are impossible or highly impracticable
- For females >12 to <17 years of age because the product will be unsafe for use in this age group.

8.4. Pregnancy and Lactation

Animal Data

The nonclinical information in [Table 54](#) was used in support of the indicated labeling sections. Additional nonclinical data are located in Sections [13.1](#) and [13.2](#), and the final labeling.

Table 54. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical data
8.1 Pregnancy	Ocular abnormalities including cataracts, opacities, exophthalmos, buphthalmos, optic nerve atrophy, retinal atrophy, lens degeneration and hemorrhage were observed in the offspring of pregnant rats administered oteseconazole from Gestation Day 6 through Lactation Day 20 at 7.5 mg/kg day (about 3.5 times the recommended human dose based on AUC comparisons). Opacities were consistently observed in pups after oteseconazole dosing of pregnant dams from the three rat strains tested: Crl:CD(SD), Crl:WI(Han) and Hsd:SD.
8.2 Lactation	There are no data available regarding the presence of oteseconazole in animal milk. It is unclear if the ocular abnormalities observed in a pre and postnatal studies resulted from pre-natal exposure or exposure via milk or both.
8.3 Females of reproductive potential	Ocular abnormalities including cataracts were observed in pre- and postnatal studies in three rat strains (see nonclinical data supporting Section 8.1 Pregnancy, above). These findings, along with a half-life of 138 days in humans, may indicate a risk to children exposed to oteseconazole <i>in utero</i> , even if the treatment with oteseconazole ended months before the patient became pregnant.

Source:
Abbreviations: AUC, area under the curve.

A total of 29 pregnancies occurred during the three phase 3 and the supportive phase 2b dose ranging clinical trials: 20 oteseconazole exposed females and 9 placebo exposed females. Among the 20 oteseconazole exposed females who became pregnant, 9 were in the phase 2b trial, with 4 of 9 subjects receiving 150 mg x 3 months (low dose); 2 of 9 subjects receiving the 150 mg x 6 months regimen (low dose); 2 of 9 subjects receiving the 300 mg x 3 months regimen (high dose) and a single subject received the 300 mg x 6 months regimen (high dose).

In light of the pre- and postnatal development ocular findings in rat pups, the Division consulted the Division of Pediatric and Maternal Health (DPMH) and the Division of Ophthalmology (DO) for input on the potential clinical implications of these nonclinical findings on oteseconazole labeling in pregnant and lactating females and females of reproductive potential.

Pregnancy

A summary of all pregnancy outcomes in the phase 1-3 trials are described below and a tabular summary of these pregnancies can be found in Section [17.5](#) in the Appendix.

There were 24 documented pregnancies in 21 oteseconazole exposed subjects in the clinical trials for whom the following outcomes were reported:

- **11 live births** (all healthy per the Applicant, 1 was preterm, 3 were Caesarean section [c/s] births)
- **7 elective terminations** (Subject (b) (6) in Trial CL-017 had two terminations; reasons for termination were not provided)
- **3 spontaneous miscarriages**
 - 1 subject in Trial CL-017 had a second pregnancy that resulted in a healthy live birth.
 - 1 subject had a spontaneous miscarriage after completing 24 weeks of the investigational product.
 - 1 subject had a chemical pregnancy. This pregnancy failed to implant after 8 weeks of exposure to oteseconazole.
- **1 subject** was in an ongoing pregnancy
- **2 subjects** were lost to follow-up

In a response to an FDA IR, the Applicant confirmed that the 11 oteseconazole exposed live births were only followed up through birth; however, the infants were not followed up post-natally for any significant periods of time. The Applicant confirmed that they attempted to contact each reporting site and noted that eight infants were reported as being healthy with no known congenital anomalies; whereas, three patients did not respond to the follow-up contact.

In their final consult evaluation to the Division, DPMH noted the following:

***DPMH Comments:** Findings of cataracts in rats in the pre- and post-natal development study raise concerns for cataract development in humans. The available data on the use of oteseconazole during human pregnancy are limited to 11 exposed pregnancies that resulted in live births. At birth, none of the exposed infants had cataracts. When the Applicant contacted the study sites in September 2021, there were eight reported healthy infants and three infants that were lost to follow-up. The follow up time varied from six months to almost six years after birth. Although, this is reassuring, it is limited to a small number of cases.*

This reviewer notes that the pathogenesis of neonatal cataracts is not well understood and may occur at variable time periods depending on the cause. Therefore, it is unclear when the injury occurred in rats. Additionally, the 11 cases of human pregnancy exposure had variable exposure times and thus variable serum concentrations during the “sensitive period.” Seven of the 11 patients received oteseconazole during the pre-pregnancy exposure window, three patients received oteseconazole during the first trimester, and one patient received oteseconazole during the 2nd and 3rd trimester.

Lactation

Of the eight patients that responded, six patients breastfed their infants, one did not, and the breastfeeding status of another patient was unknown. Of the six patients who breastfed their infants, four were currently breastfeeding their infants at the time of contact, and two breastfed their infants for a short duration (2 weeks and <3 weeks).

DPMH provided the following comments regarding oteseconazole and lactating females:

DPMH Comments: *There are no data on whether oteseconazole is present in animal milk. Because oteseconazole has a long half-life and the rats were exposed during pregnancy and lactation, it is difficult to separate the time-period.*

In his consult evaluation of the reported nonclinical findings to the review division, Dr. Wiley Chambers, the DO reviewer and Division Director noted that:

DO Comments: *Because the likelihood of developing cataracts in humans is increased in drug products which cause cataracts in nonhumans, it is often recommended that clinical trials monitor for the potential development of cataracts. There have not been enough products which cause congenital cataracts to know whether this should be recommended with drug products that cause congenital cataracts. The clinical trials with this product did not report high numbers of subjects with cataracts, but the observation period of this trial was not likely long enough to evaluate cataract development. Cataract development due to drug products is often not noticed until 12-36 months after the administration of the drug product.*

Based on the limitations of follow-up and the uncertainty of the nonclinical ocular findings, Dr. Chambers made the following conclusions and recommendations to the Division:

It is therefore not known whether the cataract findings in rats represent a risk to humans. In the absence of knowing the relevance of the finding, it is recommended that the finding be included in the package insert of the product.

The likelihood of distinguishing the etiology of any cataract development in oteseconazole treated women or their offspring is very low. Additional studies in the oteseconazole treated women and their offspring is not recommended. To collect information on children born to mothers who have taken oteseconazole, the establishment of a registry of pregnant women who have taken oteseconazole should be considered.

Following consultation with DPMH and the Division of Ophthalmology, DAI concluded that administration of oteseconazole to pregnant and lactating females of reproductive potential should be contraindicated due to the ocular abnormalities observed in the offspring of pregnant rats dosed at 7.5 mg/kg/day during pre and postnatal development. In addition, the team decided to contraindicate use of oteseconazole in this population since they considered oteseconazole's terminal half-life sufficiently prolonged to preclude use of contraceptive products within a reasonable timeframe.

9. Product Quality

The proposed drug product has been formulated as an immediate-release capsule containing 150 mg of oteseconazole drug substance. Oteseconazole capsules are lavender, hard gelatin, size 2 capsules printed with OTE 150 mg using black ink, proposed to be packaged in (b) (4) 18-count blister packages within a child-resistant carton. The NDA, as amended, has provided sufficient chemistry, manufacturing, and controls information to assure the identity, strength, purity, and quality of the proposed drug product, oteseconazole capsules. The manufacturing and testing facilities have been found acceptable and the Overall Manufacturing Inspection

Recommendation of “Approve” was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on October 5, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality; refer to the Office of Pharmaceutical Quality Integrated Assessment dated October 27, 2021, in DARRTS.

The following Post-Marketing Commitment should be included in the action letter:

Post-Marketing Commitment 4211-2: Submit the final reports and summaries of the currently ongoing ecotoxicity studies to support the categorical exclusion from an environmental assessment.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Ethics

All study protocols and amendments, as applicable, informed consent and assent (for ages 12 to 17 years) documents, and Investigator’s Brochure were approved by the appropriate Independent Ethics Committee, Institutional Review Board, or Research Ethics Board.

All phase 3 trials were conducted in accordance with International Council for Harmonization and good clinical practice requirements, the most recent guiding principles of the Declaration of Helsinki, and recommendations outlined in FDA’s guidance for industry for (acute) vulvovaginal candidiasis (August 2019), as there are no existing FDA guidances for RVVC. The supportive phase 2b dose-ranging study was also conducted in accordance with the applicable ICH Guidelines and good clinical practice. Written informed consent or assent (for ages 12 to 17 years) was obtained from all subjects.

Office of Scientific Investigations

Routine PDUFA inspections were conducted for 7 clinical investigators: Drs. Gorgacz, Miller, Kasparian, Iglesias, Moraru, Maximos, and Mosher. The inspections covered three clinical studies performed under NDA 215888: VMT-VT-1161-CL-011 (Trial CL-011), VMT-VT-1161-CL-012 (Trial CL-012), and VMT-VT-1161-CL-017 (Trial CL-017).

During their inspections, the inspectors evaluated primary efficacy endpoint source data (i.e., the investigator’s assessments of VVC signs and symptoms and mycology culture test results through Week 48 for Trials CL-011 and CL-012 and through Week 50 for Trial CL-017) which were then verified against the Applicant’s data line listings for all subjects randomized at these 7 selected sites.

Several discrepancies in the investigator's total composite VVC signs and symptoms score were noted at 5 of the 7 sites (i.e., Drs. Gorgacz, Miller, Kasparian, Iglesias, and Moraru). In addition, certified copies of the mycology culture results from the central laboratories were verified against the Applicant's data line listings for all subjects randomized at these 7 sites. One discrepancy in the mycology culture test results was noted at Dr. Gorgacz's site. These discrepancies (in the investigator's total composite VVC signs and symptoms scores and the mycology culture test results) would have no impact on the overall efficacy results of the three trials.

Two data reliability concerns related to the following were identified during the inspections:

- **Accidental unblinding events:** The Office of Scientific Investigations review team determined that accidental unblinding events were noted to have occurred as a result of an Interactive Web Response System (IWRS) programming error, impacting 6 subjects enrolled in Trials CL-011 and CL-012 at two of the 7 sites inspected (i.e., Drs. Miller and Kasparian). The Applicant stated that this IWRS programming error resulted in the unblinding of the subjects' treatment assignment for 24 subjects at 16 different sites who were enrolled between 3 Oct to 27 Nov 2018. The IWRS service provider reportedly corrected the IWRS programming error on 28 November 2018. The unblinded site staff at the 16 different sites continued to perform their delegated study-related duties. Based on these findings, the Office of Scientific Investigations review team recommended that a sensitivity analysis be conducted with regard to the efficacy data generated from the 24 subjects noted in the Applicant's 13 Sep 2021 response in order to determine the robustness of the reported overall efficacy results. Refer to Section [16.4](#) for the sensitivity analyses.
- **Subject ineligibility:** Inspectors identified that at one site (Dr. Iglesias' site), there were 4 subjects (i.e., Subjects [REDACTED] (b) (6)) who did not meet core inclusion criteria to support a history of recurrent VVC and/or diagnosis of acute VVC. These ineligible subjects were not identified during the Applicant's routine monitoring visits and were not reported to FDA in the listing of protocol deviations in the Clinical Study Report (i.e., Appendix) or the BIMO data line listing of protocol deviations (i.e., listing 7.1). Of note, according to the Clinical Study Report, all of these subjects were excluded from the modified intent-to-treat population and the per-protocol population except for Subject [REDACTED] (b) (6). This subject was included in the per-protocol population but should have been excluded.

In their concluding remarks, the Office of Scientific Investigations review team stated, "Notwithstanding the ineligible subjects, unblinding events, and recommendations noted above, the data otherwise generated by these sites appear acceptable in support of the respective indication."

Financial Disclosure Concerns

The Applicant did not identify any financial disclosure concerns that would potentially affect the interpretation of safety or efficacy for any of their phase 3 trials.

11. Advisory Committee Summary

An advisory committee was not convened for this NDA.

III. Appendices

12. Summary of Regulatory History

On March 08, 2011, Viamet Pharmaceuticals, Inc. (Viamet) submitted a request for a Pre-Investigational New Drug (PIND) meeting to discuss the development of VT-1161 capsules (b) (4). The subsequent meeting package included a synopsis of the initial clinical protocol entitled, “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single, Oral Doses of VT-1161 in Healthy Adult Subjects.” The Division granted a June 03, 2011, meeting and meeting minutes were issued on June 27, 2011.

On June 30, 2011, Viamet submitted IND 111675 for VT-1161 capsules (b) (4). The IND contained study protocol VMT-VT-1161-CL-001, entitled, “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Oral Doses of VT-1161 in Healthy Adult Subjects.” There were no clinical hold issues and the Division issued comments on their review of this initial IND on August 19, 2011.

On December 21, 2012, Viamet submitted final study reports for study VMT-VT-1161-CL-002, entitled “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Oral Doses of VT-1161 in Healthy Adult Subjects” and for study VMT-V-1161-CL-001, entitled “A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Single Oral Doses of VT-1161 in Healthy Adult Subjects.” The submission also contained a request for an End-of-Phase 1 (EOP1) meeting to discuss further development of VT-1161 and to obtain feedback on two phase 2a study protocols.

In the meeting request, Viamet proposed (b) (4) a phase 2 study in vulvovaginal candidiasis (VVC). The EOP1 meeting occurred on March 26, 2013. In the meeting minutes the Division noted their disagreement with some design elements of the proposed phase 2 studies. The Division also advised Viamet (b) (4)

On July 3, 2013, Viamet submitted protocol VMT-VT-1161-004 entitled, “A Phase 2a, Randomized, Double-Blind, Dose-Ranging Study to Evaluate the Efficacy and Safety of VT-1161 Oral Tablets Compared to Fluconazole in the Treatment of Patients with Moderate to Severe Acute Vulvovaginal Candidiasis.” The Division issued comments on August 09, 2013, noting that the study was considered purely exploratory and that more rigorous statistical testing would be needed for a more definitive trial.

On April 02, 2015, the Division issued comments on Viamet’s submissions from November 21, 2014, and January 16, 2015, that included a protocol for Study VMT-VT-1161-CL-006 entitled, “A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of VT-1161 Oral Tablets in the Treatment of Patients with Recurrent

Vulvovaginal Candidiasis.” The Division noted that the proposed trial was considered purely exploratory and that adequate control of the type I error and pre-specification of formal statistical hypothesis was expected for more definitive trials.

On September 08, 2016, Viamet requested a type C meeting to discuss the clinical development program for VT-1161 for the treatment of recurrent vulvovaginal candidiasis (RVVC) including the design of their phase 3 trials. In the comments and final meeting minutes for the December 09, 2016, meeting, the Division noted their disagreement with the proposed design of a phase 3 trial.

On September 27, 2016, Viamet was granted Fast Track (FT) and QIDP designations for treatment of VVC and treatment of recurrent vulvovaginal candidiasis.

On May 11, 2017, Viamet requested a type B, End-of-Phase 2 meeting, to discuss the proposed phase 3 development plans for VT-1161 for the treatment of RVVC. The meeting was held on May 11, 2017. In their comments the Division noted that overall, the proposed phase 3 trial design was acceptable.

The Applicant submitted an initial Pediatric Study Plan (iPSP) on October 16, 2017. The iPSP was reviewed by the Pediatric Review Committee on December 13, 2017, and comments were issued to the Viamet on December 20, 2017.

On March 15, 2018, Viamet Pharmaceuticals, Inc. informed FDA that the name of the company had changed to Mycovia Pharmaceuticals, Inc. (Applicant) effective January 2018, for oteseconazole capsule (previously identified as VT-1161 capsule; referred to as Vivjoa (oteseconazole) in this review).

The Applicant submitted an agreed iPSP on March 15, 2018. The agreed iPSP was reviewed by the Pediatric Review Committee on April 18, 2018, and the Division issued an agreement letter on April 19, 2018. The agreement included plans to enroll pediatric patients 12 to <18 years of age in the phase 3 studies and to request a partial waiver for pediatric patients less than 12 years of age in phase 3 studies.

A pre-NDA meeting was requested on August 24, 2020, to discuss chemistry, manufacturing, and controls, nonclinical and clinical data to be submitted in support of an NDA for oteseconazole. The meeting was held on November 04, 2020. The following agreements for late submissions were made: FDA agreed to accept the final report for the TQT study at the time the 120-day safety report is due and that the amendment will not result in an extension of the PDUFA date. FDA agreed to the submission of 12-month long-term data for three representative drug product stability batches within 30 days of the initial NDA submission. Mycovia confirmed the initial NDA submission would include stress conditions data, and the 6-month accelerated, and 9-month long-term data from three representative drug product batches.

On December 15, 2020, Mycovia requested a type C meeting to discuss the nonclinical pre- and post-natal (PPN) study data to be included in the upcoming NDA submission. The specific objectives of the meeting were “To obtain concurrence that the ocular findings from the pre- and postnatal development studies are not clinically relevant to humans or are not indicative of potential ophthalmic abnormalities in humans” and to “Obtain FDA’s opinion on the impact of the available pre- and postnatal development study data on labeling and NDA approvability.” The Applicant noted that “Mycovia believes findings in F1 pups observed in the Pre- and Postnatal Development study in rats in the absence of any eye related anomalies reported in

pregnancy outcomes from the clinical trials will not preclude administration of oteseconazole to women of childbearing potential.”

In the comments to the Applicant dated February 18, 2021, the Division indicated that the absence of adverse findings in newborns of mothers dosed with oteseconazole does not negate the significance of the eye related anomalies in rats since ophthalmic abnormalities did not become obvious before postnatal day 21. The Division also noted that a final decision on the labeling will be determined once all data are reviewed at the time of NDA submission. The Division restated this during the meeting that took place on February 25, 2021.

NDA 215888 for Vivjoa (oteseconazole) capsule was submitted by Mycovia Pharmaceutical, Inc., on May 27, 2021, for the proposed indication (b) (4)

(b) (4)
(b) (4) The NDA was filed on July 26, 2021. The NDA is a new molecular entity, 505(b)(1) “Program” application, and received a priority review classification.

On July 27, 2021, the Applicant proposed the tradename Vivjoa that was found conditionally acceptable on September 17, 2021.

Vivjoa was presented to the Pediatric Review Committee (PeRC) on December 14, 2021. The PeRC agreed with the Division’s recommendation to grant a full waiver for pediatric studies. For children less than 12 years of age and males of all ages, as studies are impossible or highly impracticable. For females greater than 12 to less than 17 years of age, the product will be unsafe for use.

On January 25, 2022, in response to an FDA information request, Mycovia submitted revised product labeling, including carton and container labels for the alternative dosing regimen detailed in the prescribing information. After examining this information, the Division issued an information request on January 26, 2022, detailing concerns about the proposed labeling. On January 27, 2022, the Division determined the January 25 submission constituted a major amendment and would trigger a PDUFA clock extension. The Division issued Mycovia a review extension major amendment letter on January 27, 2022, noting the new PDUFA goal date of April 27, 2022.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Primary Pharmacology

Study VMT-SU-1: Sterol 14 α -demethylase (CYP51) Inhibition by Four New Antifungal Compounds VT-1129, VT-1148, VT-1161 and VT-1163: An In

Vitro Study Utilizing Recombinant *Candida albicans* and Human CYP51 Proteins.

Key Study Findings

Oteseconazole, at 0.004 µg/ml, was shown to inhibit sterol 14-demethylation in two strains of *Candida albicans* and almost completely (94-97%) block formation of ergosterol, leading to the accumulation of lanosterol and other toxic methylated steroids.

- No discernible ligand binding was obtained for oteseconazole with Human CYP51 at drug concentrations up to 86µM
- No discernible inhibition of HuCYP51 activity was obtained with oteseconazole at drug concentrations up to 50µM.

Table 55. Sterol (%) Composition in Two Strains of *C. albicans*, (SC5314 and CA14) ± VT-1161 at 0.004 µg/ml. Maximum Values Underlined

Sterol (%)	Untreated		Oteseconazole	
	SC5314	CA14	SC5314	CA14
Ergosterol	91.6	79.6	2.6	5.0
14α-methyl fecosterol			8.6	7.5
4,14α-dimethyl cholesta 8,24-dienol			3.0	2.5
14α-methyl ergosta 8,24(28)-dien 3β 6α-diol			<u>39.8</u>	<u>60.2</u>
Lanosterol	8.4	13.2	33.2	19.9
Eburicol		7.2	12.8	5.0

Source: Reviewer generated table. Data abstracted from Table 1 Study VMT-SU-1

Table 56. Binding Parameters for Oteseconazole to *C. albicans* CYP51 (CaCYP51) and Human CYP51 (HuCYP51)

CYP Evaluated	<i>C. albicans</i> CYP51		Human CYP51	
	K _d (nM)	ΔA _{max}	K _d (nM)	ΔA _{max}
Oteseconazole	39	0.049	No binding*	No binding*

Source: Reviewer generated table. Data abstracted from Table 2 Study VMT-SU-1

*No discernible ligand binding spectrum was obtained for VT-1161 with HuCYP51 at drug concentrations up to 86µM. CaCYP51 and HuCYP51 concentrations of 5 µM were used for azole ligand binding studies. A rearrangement of the Morrison equation was used to determine K_d values of tight-binding ligand (Lutz et al. 2009). Mean K_d and ΔA_{max} values of three replicates are shown along with the associated standard errors in parentheses.

Abbreviations: A_{max}, maximum activity; CYP, cytochrome P450; K_d, equilibrium dissociation constant.

Table 57. Oteseconazole IC₅₀ Values With *C. albicans* CYP51 and Human CYP51

CYP Evaluated	<i>C. albicans</i> CYP51		Human CYP51	
	IC ₅₀ (µM)	Velocity (nmol.min ⁻¹)	IC ₅₀ (µM)	Velocity (nmol.min ⁻¹)
Oteseconazole	1.5	0.063	No inhibition*	0.1641

Source: Reviewer generated table. Data abstracted from Table 3 (incorrectly labelled Table 2) from page 39 of Study VMT-SU-1

*No significant inhibition of HuCYP51 activity was obtained with oteseconazole at drug concentrations up to 50µM

Abbreviations: CYP, cytochrome P450; IC₅₀, half maximal inhibitory concentration.

13.1.2. Secondary Pharmacology

Study # 17319: In Vitro Study of 4 Compounds

Key Study Findings

- The human melatonin MT1 receptor is among the receptors most potently inhibited by oteseconazole.

- Since published literature have shown that melatonin can play a role in cataract formation (Benitez and Carver 2019) and that melatonin receptors are present in juvenile rats (Alkozi et al. 2020), adverse eye findings in the pre and postnatal studies could theoretically involve oteseconazole inhibition of this receptor.

Table 58. In Vitro Pharmacology: Binding Assays for Select Receptors Inhibited by 10µM Oteseconazole (by Greater Than 50%)

Receptor	% Inhibition
Human adenosine A3 receptor	93 %
Human melatonin MT1 receptor	81%
Rat cerebral cortex Na ⁺ -channel (site 2)	61
Rat cerebral cortex Cl ⁻ -channel (GABA-gated)	97%
Human norepinephrine transporter,	65 %
Human dopamine transporter	71 %

Source: Reviewer generated table.

Abbreviations: Cl, calcium ion; GABA, gamma aminobutyric acid; Na, sodium.

Human melatonin MT1 receptors are among the receptors most potently inhibited by oteseconazole in this screening assay. Published literature have demonstrated melatonin receptors throughout the body including the retina and these receptors may have a role in regulating fluid pressure inside of the eye. Melatonin and analogues decrease intraocular pressure in both normotensive and hypertensive eyes (Alkozi et al. 2020). Melatonin receptors may also contribute to cataract formation (Khorsand et al. 2016).

Since MT1 melatonin receptors have been shown to be present in the juvenile rat (Ting et al. 1999), oteseconazole activity at the melatonin receptor could contribute to adverse eye findings such as exophthalmos and cataracts observed in the pre and postnatal studies in rats.

Study XT148002: In Vitro Evaluation of VT-1161 and VT-464 as Inhibitors and Substrates of Human P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 Transporters

The ability of VT-1161 (2.5 and 25 µM) to inhibit human efflux transporters, P-glycoprotein (P-gp) (MDR1/ABCB1) and breast cancer resistance protein (BCRP) (ABCG2) was evaluated by measuring the bidirectional permeability of a probe substrate (digoxin or prazosin) across a monolayer of Caco-2 and MDCKII-BCRP cells in the presence of VT-1161. Subsequently, the IC₅₀ for the inhibition of P-gp and BCRP was determined using VT-1161 concentrations of 0.1, 0.3, 1, 3, 10 and 25 µM. VT-1161 inhibited the human efflux transporter BCRP with a half maximal inhibitory concentration (IC₅₀) of 0.4 µM.

Table 59. In Vitro Inhibition of Human Transporters of Oteseconazole

Transporter	IC ₅₀ (µM)
BCRP	0.4
P-gp	2.9

Source: Reviewer generated table.

Abbreviations: BCRP, breast cancer resistance protein; IC₅₀, half maximal inhibitory concentration; P-gp; P-glycoprotein.

13.1.3. Safety Pharmacology

Table 60. Safety Pharmacology Studies

Study/ Study No.	Findings
Study 101222.WJB: Effect of VT-1161 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells	The IC ₅₀ for the inhibitory effect of VT-1161 on hERG potassium current was 1.9µM.
Study 0200RV22.002: Neuropharmacological Profile (NPP) of VT-1161 in Rats Study Species/strain: Rat, Sprague Dawley Number/sex/group: 10 males/group Doses: 0, 30, 100, 300, 1000 mg/kg/day Route of administration: Oral gavage Dosing Frequency: Once	No drug-related neuropharmacology effects were observed.
Study 1275RV22.002: Evaluation of Respiratory Function of VT-1161 Following Single-Dose Oral Administration in Sprague Dawley Rats. Species/strain: Rat, Sprague Dawley Number/sex/group: 4 males/group Dose: 0, 100, 300, 1000 mg/kg/day Route of administration: Oral gavage Dosing Frequency: Once	No biologically relevant effects on respiratory rate, tidal volume, or minute volume in conscious male rats.
Study: 1259DV22.002: Evaluation of Cardiovascular Function Following Administration of VT-1161 in Conscious Telemetered Male Beagle Dogs Species/strain: Dog, beagle Number/sex/group: 4 males/group Dose: 30, 100 and 300 mg/kg/day Route of administration: Oral gavage Dosing Frequency: Single dose	No consistent or significant drug-related effects on heart rate, or systolic, diastolic, or mean arterial blood pressure, or ECG. The average plasma concentration at 30 hours post dose for the highest (300 mg/kg) dose was 24,150 ng/mL.

Source: Reviewer generated table.

Abbreviations: AUC, area under the curve; ECG, electrocardiogram; hERG, human ether a-go-go-related gene; IC₅₀, concentration inhibiting 50% activity.

13.1.4. General Toxicology

Study 2139-002: A 26-Week Oral Toxicity Study in Rats With a 17-Week Recovery Period.

Oteseconazole dosing for 26 weeks in rats resulted in changes in the liver, adrenals, thyroid, kidneys, and ovaries with no significant effects at 0.15 mg/kg and minimal, nonadverse findings representing an extension of the drug's pharmacology or of questionable human relevance (thyroid follicular cell hypertrophy/hyperplasia, hepatocellular vacuolation, hepatocellular hypertrophy and renal tubular pigment) at 0.5 mg/kg day, about 0.2 times the maximum recommended human dosage (MRHD) based on area under the concentration-time curve (AUC) comparisons.

At doses ≥ 1.5 mg/kg/day (about 1.3 times the MRHD based on AUC comparisons, additional findings in rats included increased cholesterol, globulin, platelet counts, mild, reversible prolongations in APTT, increased organ weights (liver, thyroid, adrenal), adrenal gland vacuolation, chronic progressive nephropathy, hepatocellular hypertrophy/hyperplasia, multinucleated hepatocytes, increased Kupffer cell pigment, sex cord /stromal hyperplasia with (at 5 mg/kg) decreased prostate weight, increased lung histiocytosis, hepatocellular necrosis, increases cytochrome P450 content (+100%), Thyroxine (+525%) and Triiodothyroxine glucuronidation (+265 %).

At the end of the 17-week recovery period, increased platelet count, decreased reticulocytes and thyroid follicular hyperplasia were observed at doses ≥ 1.5 mg/kg/day while tubular pigment, hepatocellular hypertrophy, hepatocellular necrosis, multinucleated hepatocytes and pigmented Kupffer cells persisted only at 5 mg/kg (about 6 times the MRHD based on AUC comparisons). The no observed adverse effect level (NOAEL) was considered to be 0.5 mg/kg which was associated with a maximum plasma concentration (C_{max}) of 741 ng/mL and an AUC of 14,295 ng·hr/mL (about 0.2 times the MRHD based on AUC comparisons).

Table 61. Methods for Study 2139-002

Study Features and Methods	Details
Conducting laboratory and location:	(b) (4)
GLP compliance	Yes
Dose and frequency of dosing:	0, 0.15, 0.5, 1.5 and 5 mg/kg. Daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) carboxymethylcellulose (medium viscosity) in deionized water,
Species/Strain:	<i>Rattus norvegicus</i> , CD® [CrI:CD®(SD)]
Number/Sex/Group:	20 rats/sex/group
Age:	6 weeks old
Satellite groups	Recovery animals were allowed a 17-week, drug-free recovery period: Controls (10/sex), 1.5 mg/kg (10/sex) and 5 mg/kg (10/sex) Toxicokinetics rats: 6/sex/dose
Deviation from study protocol affecting interpretation of results:	No

Table 62. Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	Dose (mg/kg/day) 0 0.15 0.5 1.5 5.0
	Mortality 1 1 1 1
Clinical signs	No drug-related clinical signs
Body weights	No biologically significant drug-related effects on body weight
Ophthalmoscopy	There were no drug-related ophthalmoscopy findings
	Dose (mg/kg/day) 0 0.15 0.5 1.5 5.0
	Chorioretinal hypoplasia 2 0 2 0 0
	Retinal atrophy 1 0 0 0 0
Hematology	1.5 mg/kg: Platelets +17%, neutrophils -18%
	5.0 mg/kg: Platelets +31, Neutrophils -44%, -Hemoglobin +13%, Mean corpuscular hemoglobin -11 %.
Coagulation	1.5 mg/kg: APTT +15%
	5.0 mg/kg: APTT +27% (males)

Parameters	Major Findings
Clinical chemistry	1.5 mg/kg: Cholesterol +65%, globulin +13%, glucose -18%. 5.0 mg/kg: Cholesterol +211%, globulin +26%, A/G ratio -18%, glucose -18%, AST +36% (males), ALT +78% (males), ALP +11% (males)
Urinalysis	1.5 mg/kg: Total protein +11% 5.0 mg/kg: Total protein +12%
Gross pathology	5.0 mg/kg: Enlarged liver (2/20F), Brown kidney (2/20F)
Relative organ weights	1.5 mg/kg: Liver (+51%), thyroid (+42%), adrenals (+10%) 5.0 mg/kg: Liver (+138%), thyroid (+134%), adrenal (+47%) Kidney (+21%), prostate (-14%)
Histopathology	Adequate battery: Yes

Source: Reviewer generated table.

Abbreviations: A/G, a bumin/globulin; ALT, alanine transaminase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase.

Table 63. Histopathology Findings (Number of Animals With Findings) After 26 weeks of Dosing With Oteseconazole

Findings	OTE Dose (mg/kg/day)				
	0	0.15	0.5	1.5	5.0
Number of animals assessed	39	40	39	39	40
Adrenal (vacuolation)	0	0	0	24	38
Kidney chronic progressive nephropathy	16	18	18	34	35
Kidney tubular pigment	0	0	12	31	34
Liver hypertrophy	0	0	3	25	37
Liver multinucleated hepatocytes	0	0	0	1	28
Liver necrosis, single cell	0	0	0	0	24
Liver necrosis, subcapsular	0	0	0	0	4
Liver hepatocellular vacuolation	0	0	2	6	17
Liver hepatocellular pigment	0	0	0	2	5
Liver Kupffer cell pigment	0	0	1	4	34
Lung histiocytosis	4	1	5	7	19
Ovary (sex-cord/stromal hyperplasia)	0	0	0	7	17
Thyroid follicular cell hypertrophy/hyperplasia	0	0	10	39	40
Adrenal cortical vacuolation (electron microscopy)	-	NE	NE	NE	++

Source: Reviewer generated table.

++: Observed

Abbreviations: NE, not evaluated; OTE, oteseconazole.

Table 64. Enzyme Induction

Variable	Dose (mg/kg/day)				
	0	0.15	0.5	1.5	5.0
Cytochrome P450 content	-	NE	NE	NE	+100%
Thyroxine/triiodothyronine glucuronidation (fold induction rel. to control)	-	NE	NE	NE (triiodothyronine)	+525% (thyroxine) +265%

Source: Reviewer generated table.
Abbreviations: NE, not evaluated.

Table 65. Findings (Number Of Animals With Findings) in Recovery Animals

Findings	Dose (mg/kg/day)				
	0	0.15	0.5	1.5	5.0
Number of animals assessed	0	0	0	19	20
Kidney chronic progressive nephropathy	11	NE	NE	13	19
Kidney tubular pigment	3	NE	NE	4	14
Liver hypertrophy	0	NE	NE	0	5
Liver multinucleated hepatocytes	0	NE	NE	0	19
Liver hepatocellular pigment	0	NE	NE	0	9
Liver Kupffer cell pigment	0	NE	NE	0	15
Thyroid follicular cell hyperplasia	0	NE	NE	12	18
Platelets (10 ³ /μl)	915	NE	NE	+16%	+15%
Absolute reticulocytes (10 ³ /μl)	195	NE	NE	-24%	-19%

Source: Reviewer generated table.
Abbreviations: NE, not evaluated

After 26 weeks, mild, statistically significant prolongations in APTT were present in both sexes administered ≥ 1.50 mg/kg/day (up to +46%; prolonged by up to 7.74 seconds), relative to controls. Prolongations in APTT indicated reduced blood coagulability. A mild, statistically significant prolongation in prothrombin time was also noted in males administered 5 mg/kg/day (+12%; prolonged 1.96 seconds). No alterations in coagulation times were noted in recovery animals.

The toxicological significance of pigment deposits in the kidneys and liver is unclear. Since red blood cells are broken down by phagocytic action of Kupffer cells, where the hemoglobin molecule is split, brown pigment deposits were interpreted by the Applicant to be hemosiderin. Special stains, (Hall's bile and iron kit, Prussian blue reaction), were used on selected control and high dose animals from both sexes to further characterize the pigment present in hepatocytes, Kupffer cells and the renal tubules. Since the pigment was negative for bile and iron, the identity of the pigment remains unknown.

Microscopic lesions in the kidney at terminal necropsy included tubular pigment and exacerbation of the chronic progressive nephropathy. Chronic progressive nephropathy is a common background finding in rats and was present in all dose groups including the control group at terminal necropsy. There was an increase in the incidence/severity in both sexes at 1.5

and 5 mg/kg/day. The incidence/severity of chronic progressive nephropathy was reduced at the end of the recovery period compared to the end of dosing and was comparable to control at 1.5 mg/kg. The drug-induced exacerbation of chronic progressive nephropathy in rats may not be predictive of human toxicity since chronic progressive nephropathy has no counterpart in humans.

The significance of persistent multinucleated hepatocytes is unclear, but it was only seen in the high dose rats, is believed to be a rat-specific finding and is also seen with drugs such as rifabutin (Scampini et al. 1993). Multinucleated hepatocytes may result from the fusion of hepatocytes (Hayashi et al. 2008). There were no biologically significant increases in liver tumors in the two-year rat study of oteseconazole.

13.1.5. Pharmacokinetics

Table 66. Summary of 26-Week Oral Repeat-Dose Mean Plasma Oteseconazole Toxicokinetic Parameters in Rat

Variable	0.15 mg/kg		0.5 mg/kg		1.5 mg/kg		5 mg/kg	
	M	F	M	F	M	F	M	F
Day 1								
C _{max} (ng/mL)	25	23	104	78	234	229	791	837
T _{max} (hr)	4	6	6	4	4	6	6	24
AUC ₀₋₂₄ (ng·hr/mL)	107	157	1740	1280	4740	4230	16,600	16,300
Day 55								
C _{max} (ng/mL)	151	45	1020	471	2960	3140	11,500	13,800
T _{max} (hr)	0	4	2	4	24	2	2	6
AUC ₀₋₂₄ (ng·hr/mL)	2820	537	16,400	7640	61,500	65,900	229,000	290,000
Week 26								
C _{max} (ng/mL)	124	54	885	597	3840	4270	13,600	20,100
T _{max} (hr)	4	8	6	8	6	4	2	8
AUC ₀₋₂₄ (ng·hr/mL)	2590	880	18,600	9990	80,500	83,300	300,000	426,000
Racc	24.2	5.6	10.7	10.8	17	19.7	18.1	26.1
CL _{ss} /F (mL/h/kg)	57.9	171	26.9	50.1	18.6	18.0	16.7	11.7
t _{1/2} (h)	-	-	109	-	203	144	163	190

Source: Reviewer generated table.

Abbreviations: AUC₀₋₂₄, area under the curve from 0 to 24 hours; CL_{ss}, clearance at steady state; C_{max}, maximum plasma concentration; F, female; M, male; Racc, accumulation ratio; t_{1/2}, half-life; T_{max}, time to maximum plasma concentration.

Study # 2130-001. A 39-Week Oral Toxicity Study of VT-1161 in Dogs With a 33-Week Recovery

Key Study Findings

- Dogs were dosed with oteseconazole for 39 weeks at 0.75, 1.5, 5.5 and 17 mg/kg, equivalent to between 1 and 26 times the MRHD based on AUC comparisons
- Reversible effects seen at all doses were consistent with the pharmacology (impaired steroidogenesis) and included enlarged adrenals, increased adrenal weights, adrenal hypertrophy/hyperplasia, vacuolation, mononuclear cell infiltration increased cholesterol and reduced prostate weights. Adrenal gland ‘degeneration’ was observed in recovery animals at doses ≥5.5 mg/kg/day

- Adrenal cortical vacuoles, seen as multilamellar structures in TEM may reflect phospholipidosis, which is seen with other azoles and would not be considered adverse.
- The NOAEL was considered to be 17 mg/kg since the findings represented either an extension of the pharmacology of oteseconazole or possibly phospholipidosis which was associated with a C_{max} of 79,400 ng/mL and an AUC of 1,675,000 ng·hr/mL (about 26 times the MRHD based on AUC comparisons).

Table 67. Methods for Study 2130-001

Study Features and Methods	Details
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 0.75, 1.5, 5.5, 17
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) Carboxymethylcellulose (medium viscosity) in deionized water
Species/Strain:	Canis familiaris, beagle dog
Number/Sex/Group:	4
Age:	Approximately 5 months old
Satellite groups/ unique design:	2/sex/dose for pK at 0, 7.5 and 20 mg/kg.
Deviation from study protocol affecting interpretation of results:	No

Table 68. Observations and Results for Study 2130-001

Parameters	Major findings
Mortality	No drug-related mortality. One low dose (0.75 mg/kg) male dog # 120 sacrificed on Day 215 due to diaphragmatic herniation of abdominal organs into the thoracic cavity. One mid dose (5.5 mg/kg) male dog #139 sacrificed in extremis on Day 117 with moribundity likely due to hydrocephalus
Clinical signs	There were no drug-related effects observed in any group during the treatment period or the recovery period.
Body weights	HD: -12 % (Week 26, females)
Ophthalmoscopy	There were no drug-related effects detected by the veterinary ophthalmologist at the end of dosing or the end of the recovery period.
ECG	There were no drug-related adverse findings on the electrocardiogram evaluations. Parameters were generally comparable to controls or comparable to pretest values in the test group. For example, while QTc interval was longer than vehicle in males and females at the Week 39 predose and postdose intervals in the 17 mg/kg/day dose group, these Week 39 values were comparable to the within group pretest values.

Parameters	Major findings
Hematology	There were no biologically significant drug-related hematology changes. Parameters were generally comparable to controls or pretest values
Clinical chemistry	1.5 mg/kg: Cholesterol +35 % 5.5 mg/kg: Cholesterol +55 %, Triglycerides -12 % 17 mg/kg: Cholesterol +96 %, Triglycerides -36 %
Urinalysis	There were no biologically significant drug-related urinalysis changes.

Source: Reviewer generated table
Abbreviations: ECG, electrocardiogram

Table 69. Necropsy/Histopathology Findings

Findings	0 mg/kg	0.75 mg/kg	1.5 mg/kg	5.5 mg/kg	17 mg/kg
Gross pathology					
Enlarged adrenal glands	0/8	0/8	0/8	0/8	2/8
Organ weights					
Relative adrenal weight (Week 39)		+20%	+45%	+60%	+187 %
Relative adrenal weight (after 33-week recovery)					+30%
Relative prostate weight (Week 39)		-17%	-39%	-31%	-53 %
Relative prostate weight (after 33-week recovery)				+32%	+59%
Histopathology: Adequate battery: Yes					
Adrenal hypertrophy/hyperplasia	0/8	2/7	5/8	7/8	8/8
Adrenal mononuclear cell infiltration	0/8	1/7	2/8	4/8	7/8
Adrenal vacuolation	0/8	0/7	4/8	4/8	5/8
Adrenal gland degeneration	0	NE	NE	2	3
Electron microscopy					
Adrenal cortex vacuoles (multilamellar, membranous, likely phospholipidosis)	-	NE	NE	NE	+
Pharmacokinetics					
AUC ₍₀₋₂₄₎ ng*h/mL		56,000	181,000	641,000	1,675,000
Exposure multiple		0.9	2.8	10	20

Source: Reviewer generated table.

Besides adrenal gland 'degeneration' and a slightly increased adrenal weight, findings had resolved by recovery week 33. % indicates reduction in parameters compared to control

Abbreviations: AUC, area under the curve; NE, not evaluated.

At recovery, minimal to moderate 'degeneration' of the adrenal gland cortex was present in one male at 17.0 mg/kg/day and in all females at 5.5 and 17.0 mg/kg/day. According to the Applicant, "the degeneration consisted of cortical cells with vacuolated cytoplasm and either pyknotic or absent nuclei." Vacuolation is a prominent feature of phospholipidosis and pyknotic nuclei are often found in the adrenal gland. Since the individual animal finding was recorded as 'degeneration', it was not clear how many animals actually showed absent nuclei and if this degeneration is in fact phospholipidosis. Phospholipidosis has been observed with other azole antifungals.

13.1.6. Genetic Toxicology

Table 70. Genetic Toxicology

Study Number and Title	Key Study Findings
AD22RJ.503.BTL Bacterial Reverse Mutation Assay	Oteseconazole was tested in <i>Salmonella typhimurium</i> TA98, TA100, TA1535, and TA1537 and <i>Escherichia coli</i> strain WP2uvrA at concentrations up to 5,000 µg/plate by the Plate incorporation assay in which inverted plates were incubated for 48 to 72 hours at 37° C. Oteseconazole was not genotoxic in the bacterial mutation assay when tested (up to the maximum concentrations up to 5,000 µg/ml) either in the presence or absence of Aroclor-induced rat liver S9-mix.
GLP compliance:	Yes
Study is valid:	Yes
Study AD22RJ.341.BTL In Vitro Mammalian Chromosome Aberration Test	Oteseconazole was tested in human peripheral blood lymphocytes; up to 50 µg/mL for 4 or 20 hours without metabolic activation and up to 40 µg/mL in the presence of Aroclor-induced rat liver S9-mix. There were no statistically significant increases in the frequency of chromosome aberrations in any of the assays.
GLP compliance:	Yes
Study is valid:	Yes
Study AD22RJ.125M.BTL Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of VT-1161	Oteseconazole was evaluated in the bone marrow of male Sprague-Dawley rats 24, 48 and 96 hours after a single oral dose of 200, 400 or 800 mg/kg. Oteseconazole was negative in the bone marrow micronucleus assay since it did not induce a significant increase in the incidence of MCPes in bone marrow of male rats.
GLP compliance:	Yes
Study is valid:	Yes

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice; MCPE, micronucleated polychromatic erythrocytes.

13.1.7. Reproductive Toxicology

Study 2130-009: VT-1161: An Oral Study of Male Fertility and Early Embryonic Development in Rats

Key Study Findings

- There was no adverse effect on male reproductive function at 0.5 mg/kg/day, about 0.2 times the MRHD based on AUC comparisons.
- Increased abnormal sperm morphology, % sperm with detached head and % sperm with no hook were detected at 3 mg/kg/day, (about 1.4 time the MRHD based on AUC) and higher.
- Reduced sperm motility and sperm count were detected at 10 mg/kg/day about 7 times the MRHD based on AUC comparisons. Sperm concentration remained slightly reduced (15%) at the end of a 12-week recovery period.

Table 71. Methods of Male Fertility and Early Embryonic Development for Study 2130-009

Parameter	Method Details
Dose and frequency of dosing:	0, 0.5, 3, 10 mg/kg. Daily
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% (w/w) carboxymethylcellulose (CMC: medium viscosity) in deionized water
Species/strain:	Rattus norvegicus, Sprague Dawley
Number/sex/group:	25
Satellite groups:	Toxicokinetics animals, 5/sex/dose group
Study design:	The vehicle and test article were administered once daily to all males via oral gavage at dose levels of 0, 0.5, 3, and 10 mg/kg/day (dose volume of 10 mL/kg) at approximately the same time each day. Dosing began 42 days prior to pairing and continued to Day 75 for the main study males. The maximum pairing period was 21 days. The day on which positive evidence of copulation was observed was considered GD 0 and on GD 13, each female was euthanized, and the uterus and ovaries examined. Upon completion of most of the GD 13 uterine examinations, the first 10 main study males from the 0 and 10 mg/kg/day groups, and any surviving main study males from the 0.5 and 3 mg/kg/day groups were observed externally, euthanized, and subjected to a necropsy. During Week 23, the remaining (recovery) males were observed externally, euthanized, and subjected to a necropsy. Sperm analysis was conducted.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table
 Abbreviations: GD, gestation day.

Table 72. Observations and Results for Study 2130-009

Parameters	Major Findings			
Mortality	No drug-related mortality. One 3 mg/kg male sacrificed in extremis on Day 61 and one 10 mg/kg male found dead Day 23 (cause unknown)			
Clinical signs	No test drug-related clinical findings			
Body weights	No biologically significant drug-related changes.			
Organ weights	MD: +62% relative liver weight HD: +103 % relative liver weight			
Fertility	Fertility was unaffected by oteseconazole dosing Male mating, fertility, fecundity index was 96-100% in all groups.			
Sperm evaluations				
Oteseconazole dose	0 mg/kg	0.5 mg/kg	3 mg/kg	10 mg/kg
Total sperm count per cauda epididymis x 10 ⁸	3.2	3.6	3.2	2.4*
% normal sperm	96	96	92*	76*
Sperm motility (%)	82	85	79	61*
% detached head	4	4	7*	22*
% no hook	0.05	0.18	0.92*	1.95*
Sperm concentration (x10 ⁸ /g) cauda epididymis (Day 75)	10.9	11.7	10.5	8.7*
Sperm concentration (x10 ⁸ /g) cauda epididymis (12 weeks recovery)	10.7	-	-	9.1*
Toxicokinetics				
Day 42 AUC (ng*h/mL)	-	12,400	118,000	604,000

Source: Reviewer generated table

Abbreviations: AUC, area under the curve; HD, MD, maintenance dose.

Study 2130-008: An Oral Study of Fertility and Early Embryonic Development in Female Rats

Key Study Findings

- Maternal toxicity consisted of transient reductions in pre-mating bodyweight change at 5 and 25 mg/kg and gestational bodyweight changes at 25 mg/kg.
- Fertility index, percent post-implantation loss and mean number of early and late resorptions were numerically and statistically different from concurrent controls but were within the range of historical control values.
- The NOAEL for maternal toxicity was 1.5 mg/kg and the NOAEL for fertility and embryo-fetal development was 25 mg/kg, with an AUC estimated to be 898,600 ng*h/mL, equivalent to about 14 times the MRHD based on AUC comparisons.

Table 73. Methods of Fertility and Early Embryonic Development for Study 2130-008

Parameter	Method Details
Dose and frequency of dosing:	0, 1.5, 5 and 25 mg/kg. Daily
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water
Species/strain:	Rattus norvegicus/ CD® [CrI:CD® (SD)]
Number/sex/group:	25
Satellite groups:	None
Study design:	Female rats were dosed with oteseconazole beginning 28 days prior to pairing through GD 7. On Day 29, each female was housed in the cage of an untreated male from the same group. Positive evidence of copulation was established by a copulatory plug in the vagina and/or the presence of sperm in the vaginal lavage. The day on which evidence of copulation was observed was considered GD 0. The female was returned to an individual cage for the remainder of the study. On GD 13, each female was euthanized, the uterus and ovaries were exposed and the number of normally developing embryos, resorptions, and the total number of implantations were recorded. The number of corpora lutea on each ovary was also recorded.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table
Abbreviations: GD, gestation day.

Table 74. Observations and Results for Study 2130-008

Parameters	Major findings			
Mortality	There were no deaths during this study.			
Clinical signs	There were no drug-related clinical findings.			
Body weights				
Oteseconazole dose	0 mg/kg	1.5 mg/kg	5 mg/kg	25 mg/kg
Premating body weight change (Day 22-25)	7g	-0.2%	-87%	-94%
Premating feed consumption Week 4	19g	+1%	-7%	-11%
Gestational body weight change (GD4-7)	11g	+5%	+12%	-18%
Fertility				
Number of rats pregnant	24	25	24	19
Fertility Index (%) ^a	96	100	96	76
Necropsy findings				
Mean number of corpora lutea	15.6	16.5	16.4	15.2
Mean % post-implantation Loss ^b	3.7	4.4	2.7	9.4*
Mean number of early and late resorptions ^c	0.5	0.7	0.4	1.3*
Organ weights				
Liver weight (g)	14	+28%	+87%	+141%
Relative liver weight (liver weight/body weight)	4.4	+20%	+79%	+145%
Toxicokinetics				
Day 42 AUC ^d (ng*h/mL)	-		233,340	898,600

Source: Reviewer generated table
a: Historical control range 76-100 %
b: Historical control range 2-18 %
c: Historical control range 0.4-1.5
d: Estimated from study 0436RV22.003: A 28-Day Oral Toxicity Study with VT-1161 in Sprague Dawley Rats With a 42-Day Recovery Period
Abbreviations: AUC, area under the curve; GD, gestational day.

Study 2130-005: An Oral Study for the Effects on Embryo-Fetal Development in Rats with a Toxicokinetic Evaluation.

Key Study Findings

- There were no drug-related malformations or abnormalities in this study
- Bodyweight gain (GD0 to GD20) was reduced by 11% in high dose dams.
- The NOAEL for maternal toxicity was 10 mg/kg and the NOAEL for embryo-fetal development was 40 mg/kg, with an AUC estimated to be 885,000 ng*h/mL, equivalent to about 14 times the MRHD based on AUC comparisons.

Conducting laboratory and location:



GLP compliance: Yes

Table 75. Oral Embryo-Fetal Development Study Design

Methods	
Dose and frequency of dosing:	0, 3, 10 and 40 mg/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water
Species/Strain:	Rattus norvegicus/ Sprague Dawley
Number/Sex/Group:	25/dose group
Satellite groups:	Toxicokinetics animals 3-5/dose group
Study design:	Oteseconazole was administered once daily from GD 6 to 17 via oral gavage at 3, 10, and 40 mg/kg/day at 10 mL/kg to pregnant rats. On GD 20, each main study female was euthanized by carbon dioxide inhalation. The uterus was excised, and the gravid uterine weight was recorded, the location of viable and nonviable fetuses, early and late resorptions for each uterine horn, and the total number of implantations were recorded. The number of corpora lutea on each ovary was also recorded.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table

Abbreviations: GD, gestation day.

Table 76. Rat Oral Embryo-Fetal Study Findings

Parameters	Major Findings
Mortality	There were no drug-related deaths during the study
Clinical signs	There were no drug-related clinical signs during the study. Animals were observed at least twice daily with detailed clinical observations daily from GD 6 through 20.
Food consumption (GD 0-20)	HD: -15%. Food consumption was measured on GD 0 and daily from GD 6 to 20.
Body weight gain GD 0- GD20	HD: -11%
Body weight	There were no biologically significant differences in bodyweights (measured on GD 0 and daily from GD 6 to 20) between treated and control animals.
Number pregnant	24, 24, 24 and 25 (out of 25/group)
Necropsy findings Cesarean section data	There were no significant differences in cesarean section data (implantation sites, corpora lutea, preimplantation loss, viable fetuses, post-implantation loss, early resorptions, late resorptions) between drug treated and control animals.
Necropsy findings Offspring	There were no significant increases in external, visceral, or skeletal malformations at any oteseconazole dose.

Source: Reviewer generated table
Abbreviations: GD, gestation day.

One control fetus had a malformed palate. One 40 mg/kg/day fetus showed several external malformations including gastroschisis, edema (entire body), brachydactyly (hind limbs), syndactyly (hind limbs), and hind limbs malrotated. This animal also showed skeletal malformations (femur, fibula, tibia misshapen and tibia bent). One additional fetus at 40 mg/kg/day was observed with fused sternbrae. These findings were rare, not observed in concurrent controls, and were only seen in one fetus. All except hind limb brachydactyly have been observed within recent historical control data for this laboratory. The finding is not clearly related to the test article.

Visceral malformations observed at 40 mg/kg included absent thyroid and situs invertus (arrangement of the internal organs is a mirror image of normal anatomy in the abdomen and thoracic cavity), but the incidences were comparable to historical controls for this laboratory. A statistically significant increase in rudimentary ribs was observed at 40 mg/kg/day (60% compared to 29% in controls) but this value is within recent historical control data. These findings were not considered drug related.

Table 77. Toxicokinetics Estimated for Embryo-Fetal Development Study in Rats

Parameter	0 mg/kg	3 mg/kg	10 mg/kg	40 mg/kg
Day 17 AUC (ng*h/mL)	-	79,000	254,000	885,000
Exposure multiple		1	3	10

Source: Reviewer generated table.
Abbreviations: AUC, area under the curve.

Study 2130-007: VT-1161: An Oral Study for Effects on Embryo-Fetal Development in Rabbits with a Toxicokinetic Evaluation

Key Study Findings

- Abortions and reduced fetal weights were observed at the highest dose tested, (15 mg/kg), in the presence of maternal toxicity (reduced bodyweight gain and food consumption)

NDA 215888
Vivjoa (oteseconazole)

- There were no increases in malformations or abnormalities in drug-treated animals
- The NOAEL for maternal toxicity was 5 mg/kg and the NOAEL for embryo-fetal development was 15 mg/kg, with an AUC estimated to be 470,000 ng*h/mL, equivalent to about 7 times the MRHD based on AUC comparisons.

Conducting laboratory:



GLP compliance: Yes

Table 78. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency	0, 2, 5, and 15 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water
Species/Strain:	<i>Oryctolagus cuniculus</i> New Zealand White rabbit Hra:(NZW)SPF
Number/Sex/Group:	20/group
Satellite groups:	3-4 toxicokinetics animals/dose group
Study design:	Oteseconazole was administered once daily from GD 7 to 19 via oral gavage at 2, 5, and 15 mg/kg/day to pregnant rabbits. Observations of the animals included clinical signs, body weights, and food consumption, and in addition, gross anatomical pathology, and a cesarean section on GD 29. Blood was collected on GD 7 and 19 for determination of the toxicokinetic profile of oteseconazole from all TK animals, and single blood samples were collected on GD 29 for determination of plasma oteseconazole concentrations from the first four main study animals at 2, 5, and 15 mg/kg/day. All fetuses were weighed, sexed, and given the appropriate external, visceral, or skeletal examination.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table

Abbreviations: GD, gestation day; TX, toxicokinetic.

Table 79. Observations and Results for Study 2130-007

Parameters	Major Findings
Mortality	At 15 mg/kg/day, four rabbits aborted on GD 25, GD 26, GD 27, and GD 25 and one delivered early prior to euthanasia on GD 29. Animals that aborted were euthanized on the same day. All other animals survived.
Clinical signs	At 15 mg/kg/day, test article-related observations consisted of decreased activity (one animal on GD 17-22), absent/few feces (13 animals beginning on GD 12), red material in pan on GD 25-27 (five animals [four of which aborted or delivered early]), and thin appearance beginning on GD 21 (11 animals). Similar test article-related findings were observed at 2 and 5 mg/kg/day, but were transient in nature, observed at a low incidence (1-4 days per animal), and not considered adverse.
Body weights	HD: -6 % GD 29
Body weight gain	HD: -35%, GD 29
Food consumption	HD: -26 % GD 0 to GD 29
Necropsy findings Cesarean section data	No significant effects on number of corpora lutea, implantation sites, viable fetuses, sex ratio, post-implantation loss, litter size, early resorptions, late resorptions at any dose compared to control.
Necropsy findings Offspring	LD: micrognathia in one animal HD: -12 % reduced fetal body weights Micrognathia not seen in historical controls at this lab but was only seen in one low-dose animal. Micrognathia has been reported in historical control New Zealand White rabbits in published literature (Ema et al. 2012). Other findings were seen at a low incidence, similar to controls or within the range of historical control data and not considered test article related.

Source: Reviewer generated table
Abbreviations: GD, gestation day.

Table 80. Oteseconazole Pharmacokinetics in Pregnant Rabbits

Parameter	0 mg/kg	2 mg/kg	5 mg/kg	15 mg/kg
Day 19 AUC (ng*h/mL)	-	50,000	137,000	470,000
Exposure multiple		0.6	1.6	5.5

Source: Reviewer generated table
Abbreviations: AUC, area under the curve.

Study 1234001: An Oral (Gavage) Study of the Effects of VT-1161 on Pre- and Postnatal Development, Including Maternal Function and Toxicokinetics, in Rats.

Key Study Findings

- Drug-related increases in opacities and exophthalmos were observed at 7.5 mg/kg, a dose equivalent to 3.5 times the clinical exposure based on AUC comparisons
- Oteseconazole concentration in pup plasma was 2 to 5 times maternal plasma concentration and declined between Day 4 and Day 21.
- The NOAEL for maternal toxicity was 7.5 mg/kg and the NOAEL for pre- and post-natal development was 3 mg/kg (AUC of 57,833 ng*h/mL, an exposure similar to the clinical exposure)

Conducting laboratory and location:



(b) (4)

GLP compliance: Yes

Table 81. Methods of Oral Pre and Postnatal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 1, 3 and 7.5 mg/kg. Daily.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% Carboxymethylcellulose (CMC, medium viscosity) in deionized water
Species/strain:	Rattus norvegicus, CrI:CD(SD)
Number/sex/group:	23 pregnant females/group
Satellite groups:	4-8 Toxicokinetics animals/group
Study design:	Pregnant F0 females were dosed via oral gavage once daily from Gestation Day 6 through Lactation Day 20. Mortality, clinical signs, body weights, body weight gains, food consumption, parturition, toxicokinetics, and gross necropsy findings were evaluated in these dams. The F1 offspring were assessed for viability, survival, clinical signs, body weights, body weight gains, developmental landmarks, neurobehavior, estrous cyclicity, reproductive performance including mating, fertility, and copulation time, sperm motility, epididymal sperm count, and sperm morphology, gross necropsy, toxicokinetics, and male reproductive organ weights. Intrauterine survival was evaluated for the F2 embryos including pre- and post-implantation loss.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table.

Table 82. Observations and Results in Oral Pre and Postnatal Developmental Study in Rats

Parameters	Major Findings
F ₀ Dams	
Clinical signs:	No drug-related clinical signs
Body weight:	No drug-related effects in gestational or lactation bodyweights
Feed consumption:	No drug-related effects in gestational or lactation feed consumption
Uterine content:	No drug-related effects on the number of former implantation sites or the number of unaccounted-for sites in the uterus.
Necropsy observation:	No drug-related gross findings
Toxicokinetics:	Table 83. Toxicokinetics

Parameter	1 mg/kg	3 mg/kg	7.5 mg/kg
AUC GD 6 (ng*h/mL)	3510	14000	36200
AUC GD 18 (ng*h/mL)	30500	129000	297000
AUC LD 20 (ng*h/mL)	5570	30500	97500

Source: Reviewer generated table

Dosing Solution Analysis	The analyzed dosing formulations generally contained 93.6% to 100.6% of the target concentration except for the last preparation of the 0.1 mg/mL, used for the 1 mg/kg animals between lactation days 14-21, which was 72.9% of target concentration. Since the solution was only used for a limited period, was ~12% outside of the acceptable range (85 to 115% of target concentrations), and since the higher doses were unaffected, this error did not affect the interpretation of the study.

F ₁ Generation	

Parameters	Major Findings																				
Survival	Table 84. Survival in F1 Pups (% per Litter) <table border="1"> <thead> <tr> <th>Dose (mg/kg)</th> <th>0</th> <th>1</th> <th>3</th> <th>7.5</th> </tr> </thead> <tbody> <tr> <td>Postnatal Survival to PND 4 (% per litter)</td> <td>99</td> <td>99</td> <td>96</td> <td>97</td> </tr> <tr> <td>Postnatal Survival PND 4 to Weaning (% per litter)</td> <td>99</td> <td>100</td> <td>99</td> <td>98</td> </tr> </tbody> </table>	Dose (mg/kg)	0	1	3	7.5	Postnatal Survival to PND 4 (% per litter)	99	99	96	97	Postnatal Survival PND 4 to Weaning (% per litter)	99	100	99	98					
Dose (mg/kg)	0	1	3	7.5																	
Postnatal Survival to PND 4 (% per litter)	99	99	96	97																	
Postnatal Survival PND 4 to Weaning (% per litter)	99	100	99	98																	
Clinical signs:	Table 85. Clinical Signs in F1 Pups <table border="1"> <thead> <tr> <th>Dose (mg/kg)</th> <th>0</th> <th>1</th> <th>3</th> <th>7.5</th> </tr> </thead> <tbody> <tr> <td>Lens opacity</td> <td>0</td> <td>0</td> <td>1(1)</td> <td>3(3)</td> </tr> <tr> <td>Exophthalmos</td> <td>0</td> <td>0</td> <td>(0)</td> <td>9(8)</td> </tr> <tr> <td>Dark red discoloration</td> <td>0</td> <td>0</td> <td>0</td> <td>2</td> </tr> </tbody> </table> Opacity Opacity/exophthalmos first noted on Day 21 One TK phase female in the 3 mg/kg/day group had bilateral opacity on PND 21	Dose (mg/kg)	0	1	3	7.5	Lens opacity	0	0	1(1)	3(3)	Exophthalmos	0	0	(0)	9(8)	Dark red discoloration	0	0	0	2
Dose (mg/kg)	0	1	3	7.5																	
Lens opacity	0	0	1(1)	3(3)																	
Exophthalmos	0	0	(0)	9(8)																	
Dark red discoloration	0	0	0	2																	
Body weight:	Table 86. Bodyweights in F1 Pups <table border="1"> <thead> <tr> <th>Dose (mg/kg)</th> <th>0</th> <th>1</th> <th>3</th> <th>7.5</th> </tr> </thead> <tbody> <tr> <td>PND 21 Pup Body Weight g (%) b</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Males</td> <td>51</td> <td>+2%</td> <td>-3%</td> <td>-8%</td> </tr> <tr> <td>Females</td> <td>50</td> <td>+2%</td> <td>-4%</td> <td>-8%</td> </tr> </tbody> </table>	Dose (mg/kg)	0	1	3	7.5	PND 21 Pup Body Weight g (%) b					Males	51	+2%	-3%	-8%	Females	50	+2%	-4%	-8%
Dose (mg/kg)	0	1	3	7.5																	
PND 21 Pup Body Weight g (%) b																					
Males	51	+2%	-3%	-8%																	
Females	50	+2%	-4%	-8%																	
Physical development:	There were no drug-related effects on the mean age of attainment of balanopreputial separation or vaginal patency.																				
Neurological assessment:	There were no biologically significant, drug-related effects on auditory startle response, motor activity, biel maze swimming trials.																				

Table 87. Summary of Pup Litter Plasma Oteseconazole Concentrations on Day 4 and Day 20

Maternal Dose* (mg/kg)	Day	Time Postdose (h)	Pup litter concentration (ng/mL)	Pup litter: dam concentration ratio
1.0	PND 4	4	2050	2.56
1.0	PND 20	4	500	1.57
1.0	PND 20	24	580	3.93
3.0	PND 4	4	8910	2.8
3.0	PND 20	4	4430	3.0
3.0	PND 20	24	4560	4.7
7.5	PND 4	4	31,500	2.4
7.5	PND 20	4	19,400	4.0
7.5	PND 20	24	16,000	5.2

Dams were dosed from GD6 to Lactation day 21.

Table 88. Summary of Pup Litter Plasma Oteseconazole Concentrations for PND 35, 85, and 120

Study Day	PND 35	PND 85	PND 120
Dose (mg/kg/day)	Pup litter oteseconazole concentration (ng/mL)		
1.0	0.0	0.0	0.0
3.0	0.0	0.0	0.0
7.5	136	0.0	0.0

F1 Reproduction	No biologically significant drug-related effects on gestation, estrous cyclicity, reproductive performance (mating index or fertility index in males or females, male copulation index, female conception index or precoital interval) or sperm evaluations
F2 Generation	No significant effects on mean number of corpora lutea, implantations, pre-implantation loss, number of live conceptuses per litter, number of early resorptions per litter, number of dead conceptuses or mean % post implantation loss

Source: Reviewer generated table

Abbreviations: AUC, area under the curve; GD, gestational day; LD, lactation day; PND, postnatal day

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Carcinogenicity

Study 2130-018: A 104-Week Oral Carcinogenicity Study in Rats.

Key Study Findings

- Excess mortality was observed in rats dosed at 5 mg/kg and the high dose was subsequently reduced to 3 mg/kg at Week 33 for males and Week 55 for females. Based on high mortality, all males were terminated between Weeks 77 (5/3 mg/kg) and 90 and all females were terminated between Weeks 84-86.
- Hemorrhage was increased in the adrenals, brain, coagulating gland, ears, epididymis, head, heart, lung, nose pancreas, prostate, seminal vesicles, spinal cord, testes, thymus, and urinary bladder in male rats with a few cases of hemorrhage in the brain, lung, and pancreas in females.
- Statistically significant increases in thyroid follicular cell adenomas and combined thyroid follicular cell adenoma and carcinoma in both males and females, at 1.5 mg/kg and above (AUC exposure similar to the exposure at recommended human dose) and thyroid follicular cell carcinoma in HD females at 5 mg/kg/day, (AUC exposure about 7 times the exposure at the recommended human dose)

Table 89. Tumor Types With p values ≤0.05 for Dose-Response Relationship or the Pairwise Comparisons in a 104-Week Oral Carcinogenicity Study in Rats

Sex	Organ Name	Tumor Name	0 mg	0.5 mg	1.5 mg	5/3 mg
			Vehicle Cont (N=70) P - Trend	Low (N=70) P - C vs. L	Med (N=70) P - C vs. M	High (N=70) P - C vs. H
Male	Liver	Adenoma, hepatocellular, benign	0/70 (29) 0.1263	4/70 (33) 0.0734	8/70 (35) 0.0053*	2/70 (16) 0.1212
		Adenoma, hepatocellular, benign/malignant	1/70 (29) 0.0804	4/70 (33) 0.2201	8/70 (35) 0.0273@	3/70 (16) 0.1212
	Testes	Adenoma, Leydig cell, benign	1/70 (29) <0.0001*	5/70 (33) 0.1300	12/70 (38) 0.0033*	15/70 (25) <0.0001*
		Adenoma, follicular cell, benign	2/70 (29) <0.0001*	6/70 (34) 0.1860	36/70 (50) <0.0001*	27/70 (33) <0.0001*
	Thyroid gland	Carcinoma, follicular cell, malignant	1/70 (29) 0.0162@	2/70 (32) 0.5375	13/70 (37) 0.0014*	4/70 (17) 0.0549
		Adenoma, follicular cell, benign/ malignant	3/70 (30) <0.0001*	8/70 (35) 0.1477	44/70 (53) <0.0001*	29/70 (34) <0.0001*
	Female	Liver	Carcinoma, hepatocellular, malignant	0/70 (26) 0.0169*	0/70 (28) NC	0/70 (30) NC
Adenoma, follicular cell, benign			0/70 (26) <0.0001*	2/70 (29) 0.2734	12/70 (37) 0.0007*	28/70 (43) <0.0001*
Thyroid gland		Carcinoma, follicular cell, malignant	0/70 (26) 0.0010*	0/70 (28) NC	2/70 (32) 0.3001	6/70 (32) 0.0224*
		Adenoma/carcinoma, follicular cell, benign/malignant	0/70 (26) <0.0001*	2/70 (29) 0.2734	13/70 (37) 0.0003*	32/70 (45) <0.0001*
Uterus with Cervix		Granular cell tumor, benign	2/70 (28) 0.0018*	1/70 (29) 0.8880	6/70 (34) 0.2003	10/70 (34) 0.0269@

Source: Reviewer generated table based on Table generated by Mathematical Statistician, Dr Malick Mbodj

*Statistically significant at 0.005 and 0.025 level for common tumors and rare tumors for tests of dose response relationship and 0.01 and 0.05 level for common tumors and rare tumors for pairwise comparisons respectively

Table 90. Incidence of Hemorrhage in Rats After Dosing at 5/3 mg/kg/day for 77 Weeks (Males) or 86 Weeks (Females)

Organ system	Control	1.5 mg/kg	5/3 mg/kg
Adrenal	0	0	7
Bone marrow, femur	0	1	1
Bone marrow, sternum	0	0	2
Brain (1 low also) mostly minimal and mild	0/0	1/0	13 (+2 females)
Coagulating gland (1L)	0	1	4
Ears		0	7
Epididymis	0	0	13
Esophagus	0	0	1
Foot		0	2
Head	0	0	4
Heart	0	0	6
Larynx (1L)	0	0	2
Lung (1L)	0	2	3 (+3 females)
Sciatic nerve	0	0	1
Nose	0	0	10
Pancreas	0	0	2 (+2 females)
Pancreas islet	9	10	37
Pharynx	0	0	3

Organ system	Control	1.5 mg/kg	5/3 mg/kg
Prostate (1)	0	1	10
Seminal vesicles	0	0	5
Skeletal muscle degeneration	0	1	1
Skin	0	0	2
Spinal cord	0	0	6
Stomach	0	0	2
Testes	0	0	7
Thymus	0	0	6
Thyroid	0	0	2
Urinary bladder	0	1	6

Source: Reviewer generated table.

Discussion

Thyroid follicular cell tumors are not uncommon in drugs with increased T3 turnover by the liver and these may be secondary to chronic thyroid follicular cell stimulation (Hood et al. 1999). In male and female rats administered oteseconazole at 5 mg/kg/day for 26-weeks, there were 4- to 8-fold increases in liver T4 glucuronidation activities and 2- to 5-fold T3 glucuronidation activities compared to concurrent control animals. The rat is believed to be highly sensitive to the development of thyroid follicular cell tumors as this species lacks T4-binding globulin, the high affinity plasma protein which carries 70% of human T4 and T3. Instead, the rat relies upon the lower affinity transthyretin and albumin as a buffer for alterations in thyroid hormone concentrations. This reduced buffering capacity in the rat causes greater fluctuations in free T4 and T3 and therefore a greater sensitivity for TSH release when levels of these hormones are reduced. There were no thyroid tumors in Tg.rasH2 mice exposed to oteseconazole for 26 weeks. The development of thyroid tumors secondary to selective induction of liver metabolism appears to be unique to the rat and may have reduced relevance in predicting human carcinogenicity (Bartsch et al. 2018). The human relevance of the increase in thyroid follicular cell tumors is unclear.

The Applicant also takes the position that the development of Leydig cell tumors in the rat is a result of inhibition of testosterone by oteseconazole and a consequent release from feedback inhibition on luteinizing hormone release from the pituitary resulting in overstimulation of the Leydig cells and development of hyperplasia and adenoma. This mechanism is considered plausible as compounds which interfere with testosterone synthesis are associated with an increase in luteinizing hormone levels and the development of this tumor. Support for this mechanism in rats administered oteseconazole was directly tested in study No. 2130-019. A decrease in group mean serum testosterone concentrations (-80%) and increase in luteinizing hormone was observed at 100 mg/kg/day which correlated with changes in the testes, prostate and seminal vesicles/ coagulating glands generally associated with testosterone deficiency.

Hemorrhage was increased in the adrenals, brain, coagulating gland, ears, epididymis, head, heart, lung, nose pancreas, prostate, seminal vesicles, spinal cord, testes, thymus, and urinary bladder in male rats with a few cases of hemorrhage in the brain, lung, and pancreas in females. In contrast, there was no drug-related increase in hemorrhage in the 39-week dog study and the 26-week rat study. and coagulation parameters were only mildly affected. The brain was within normal limits at 5 mg/kg in males and females at the end of 26 weeks in rats.

Study 2130-025. VT-1161: A 26-Week Oral Oncogenicity Study in CByB6F1-Tg(HRAS)2Jic[rasH2] Transgenic Mice

Key Study Findings

- There were no oteseconazole-related tumors in male and female TgrasH2 mice.
- TgrasH2 mice received once daily oral gavage doses of 0 (control), 0.5, 1.5, or 5 mg/kg/day (males) and 0 (control), 1.5, 5, or 15 mg/kg/day (females) oteseconazole in 0.5% carboxymethylcellulose for 26 weeks. There were no statistically significant increases in tumors compared to controls and no tumors which increased with a statistically significant dose response relationship in male or female mice.

13.2.2. General Toxicology; Additional Studies

Study #2130-019: Effect of VT-1161 on the Male Reproductive System in Rats.

Table 91. Summary of Effects on Reproductive Hormones Measured by Enzyme-Linked Immunosorbent Assay and LC-MS/MS

Hormone	30 mg/kg	100 mg/kg
Antech GLP enzyme-linked immunosorbent assay		
Testosterone	+1%	-64%
Luteinizing hormone	+12%	+45%
Follicle stimulating hormone	+7%	+43%
OpAns (LC-MS/MS)		
Progesterone	-23%	+119%
17-OH progesterone	-28%	-48%
Androstenedione	+37%	-47%
Testosterone	-38%	-80%
DHT	-35%	-45%
DHEA	-43%	-32%
Estrone	-44%	-33%
Estradiol	-44%	-32%

Source: Reviewer generated table.

Abbreviations: DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; GLP, good laboratory practice; LC-MS/MS, liquid chromatography with tandem mass spectrometry.

Groups of male and female Sprague Dawley rats were administered 30 or 100 oteseconazole by oral gavage once daily for 7 days. Oteseconazole doses of 30 or 100 mg/kg/day were associated with reproductive hormone changes at 30 and 100 mg/kg/day that suggested disrupted testosterone biosynthesis. Effects included decreased serum 17 α -hydroxyprogesterone, androstenedione (100 mg/kg/day only), testosterone and dihydrotestosterone concentrations, and a compensatory increase in luteinizing hormone and progesterone concentrations (100 mg/kg/day only). Serum follicle stimulating hormone concentration was also mildly increased at 100 mg/kg/day. Microscopic findings consistent with testosterone deficiency were observed in the male reproductive tract at 100 mg/kg/day.

13.2.3. Reproductive Toxicology: Additional Studies

Study 01234002: A Study of Postnatal Ocular Development in Rat Offspring Following Maternal Oral Administration of VT-1161 During Pregnancy and Lactation.

Key Study Findings

- Increased drug-related mortality was observed post-weaning (postnatal day [PND] 21-23) in oteseconazole-treated animals associated with microchip implantation. This degree of excess mortality was not seen in a subsequent study at the same dose.
- Decreased erythrocyte mass (red blood cell count, hemoglobin, and hematocrit, with macrocytosis and anisocytosis) was observed in surviving F1 males and females on PND 24-25 with an increase in absolute reticulocyte count at PND 24-25 but hematology parameters were comparable to controls on PND 61.
- Cataracts were increased in drug-treated animals at all time points evaluated (PND 15-18, 26-30 and 50-55). Hemorrhage and hyphema were also observed in some animals.

Conducting laboratory and location:



GLP compliance: Yes

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Table 92. Methods for Study 01234002

Dose and frequency of dosing:	0, 7.5 mg/kg. Daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/w) carboxymethylcellulose in deionized water
Species/Strain:	Rattus norvegicus/Crl:CD(SD)
Number/Sex/Group:	22
Satellite groups:	None
Study design:	Pregnant rats were dosed via oral gavage daily from Gestation Day 6 through Lactation Day 20. Mortality, clinical signs, body weights, body weight gains, food consumption, and parturition were recorded. The offspring were evaluated for litter viability and survival, clinical, signs, body weights, body weight gains, eye opening, ophthalmology, clinical pathology (hematology and coagulation), macroscopic necropsy, brain weight, and microscopic pathology of the eyes, optic nerves, and gross lesions). On PND 4 the heads of 49 controls and 46 oteseconazole-treated pups were collected and preserved. Intact offspring that were found dead or euthanized for humane reasons during PND 0–4 were necropsied and heads collected. On PND 24-25, (and for all unscheduled deaths) necropsies were performed and tissues** including eyes, optic nerves, and gross lesions were collected from control and drug-treated animals (10/sex/dose group). On PND 61-62, necropsies were performed, organs weighed and tissues** collected from the 1 animal/sex/litter selected for clinical pathology (of 90 and 86 males and female controls and 48 and 52 male and female drug-treated animals.
Protocol deviations affecting interpretation of results:	None

Source: Reviewer generated table

**The following tissues were collected for all animals at the PND 24–25 necropsy and from the 1 animal/sex/litter selected for clinical pathology on PND 61–62: Cranium, bone marrow smear, bone with marrow (femur), brain, heart, kidneys, liver, eyes with optic nerve (2), pituitary gland, spleen, skeletal muscle, stomach, thymus, and all gross lesions (all groups).

Abbreviations: PND, postnatal day.

Table 93. Observations and Results for Study 01234002

Parameters	Major Findings
F0 animals	All F ₀ maternal females survived to scheduled euthanasia and no biologically significant drug-related clinical signs or body weight changes were observed
F1 Survival to PND 4	Control: 90 % Oteseconazole: 97%
F1 survival PND 4 to weaning	Control: 100 % Oteseconazole: 95%
Postweaning mortality	Control: 0. Oteseconazole: 84 Mortality/moribundity was observed for 84 rats (46 males, 38 females) from 18 of 22 litters during PND 21-23 following bleeding from the microchip implantation site. Dark red contents were observed for the dorsal thoracic or lumbar skin of 44 and 38 of these males and females, correlating to microscopic findings of skin hemorrhage. Dark red areas and/or discoloration in the cranium (surrounding brain; 2/46 males; 3/38 females, eyes (4/46 males; 1/38 females), and skeletal muscle (3/46 males; 3/38 females) also correlated to hemorrhage. Two animals had dark red stomach contents, with no evidence of ulcers.
Clinical signs	Clinical observations in animals that died included hypoactivity, piloerection, cool or pale body or extremities, labored respiration, and decreased respiration rate.

Parameters	Major Findings	
Body weights of drug treated animals compared to controls on PND 21	Males: -8% Females: -6%	
Hematology	Table 94. Hematology in Rat Pups on PND 24-25	
	Laboratory test	Control
		7.5 mg/kg
	RBC (mil/ μ L)	5.8
	HGB (g/dL)	11.3
	HCT (%)	41.2
	RETIC ($10^3/\mu$ L)	1374
	MCHC (g/dL)	27
	RDW (%)	20
	PLT ($10^3/\mu$ L)	1030
		4.7 (-19%)
		8.7 (-23%)
		35 (-16%)
		1645 (+20%)
		25 (-8%)
		28 (+35%)
		1683 (+63%)
	No differences in hematology were observed on PND 61	
Ophthalmoscopy examinations	Table 95. Ophthalmic Findings PND 15-18	
	Finding	0 mg/kg
		7.5 mg/kg
	Number examined	196
	Cataract-bilateral	3
	Cataract-unilateral	0
	Hyphema-unilateral	0
	Hemorrhage, vitreous unilateral	0
		209
		2
		8
		1
		2
	Table 96. Ophthalmic Findings PND 26-30	
	Finding	0 mg/kg
		7.5 mg/kg
	Number examined	176
	Cataract-bilateral	0
	Cataract-unilateral	0
	Hyphema-unilateral	0
	Hemorrhage, vitreous unilateral	0
	Hemorrhage iris	1
	Lens luxation	0
		100
		5
		5
		1
		1
		0
		2
	Table 97. Ophthalmic Findings PND 50-55	
	Finding	0 mg/kg
		7.5 mg/kg
	Number examined	176
	Cataract-bilateral	0
	Cataract-unilateral	0
	Hemorrhage, vitreous unilateral	0
		100
		7
		12
		1
Notable gross necropsy findings F1 pups	Table 98. Necropsy Findings	
	Finding	0 mg/kg
		7.5 mg/kg
	Dark red contents of skin	1/20
		15/20
	Dark red contents of the skin (dorsal thoracic region and ventral surface) were seen in oteseconazole treated animals. This location correlated with the scapular microchip implantation site.	

Source: Reviewer generated table

Abbreviations: HCT, hematocrit; HGB, hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet; PND, postnatal day; RBC, red blood cell; RDW, red cell distribution width; RETIC, reticulocyte count.

Study 01234003: An Investigative Study of the Effects of VT-1161 on Postnatal Development in Rats

Key Study Findings

- Oteseconazole was administered to pregnant and lactating rats at 7.5 mg/kg/day which resulted in reduced bodyweights (up to -16%), lens opacities, swollen eyes, hemorrhage, hyphema, buphthalmos and corneal ulceration on PND 21 and PND 34. Postmortem findings included retinal and optic nerve atrophy as well as lens degeneration.
- Clinical chemistry changes on PND 21 included a markedly increased GGT titer, increased prothrombin time and APTT which reversed by PND 34
- Overall mortality in pups was comparable to control and reduced compared to Study 1234002

Conducting laboratory location:



GLP compliance: Yes

Table 99. Methods of Oral Pre and Postnatal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 7.5 mg/kg. Daily.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% Carboxymethylcellulose (CMC, medium viscosity) in deionized water
Species/strain:	Rattus norvegicus, CrI:CD(SD)
Number/sex/group:	22 pregnant females/group
Satellite groups:	None
Study design:	The test article and vehicle were administered to the F0 females by oral gavage dose from Gestation Day 6 through Lactation Day 20. Mortality, clinical signs, body weights, body weight gains, food consumption, and parturition were recorded for F ₀ animals. Litter viability and survival, clinical signs, body weights, body weight gains, ophthalmology, and clinical pathology (PND20-21 and PND 33-34) were recorded for F1 animals. To reduce variability among the F1 litters, 8 pups/litter of equal sex distribution, if possible, were randomly selected on PND 7 with the exception that any pup observed with an abnormality of the eyes was retained. Following collection of blood samples for Hematology, Coagulation, and clinical chemistry, 2 pups per litter (1 pup/sex/litter, if possible) had whole carcasses retained in 10% neutral-buffered formalin for possible future histopathology. Remaining culled pups were discarded without further examination. Ocular examinations were conducted by a board-certified veterinary ophthalmologist during PND 20–21 and PND 33–34. On PND 21 approximately half of the pups selected to comprise the post-weaning F1 generation from each litter were identified with a subcutaneous microchip and the other half were identified with an ear tag, across both sexes as possible. Macroscopic necropsy, and a limited tissue microscopic pathology were collected for F1 animals.

Parameter	Method Details
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table
Abbreviations: PND, postnatal day.

Table 100. Observations and Results for Study 01234003

Parameters	Major findings
F0 Dams	No biologically significant drug related effects on mortality, clinical signs, body weights, food consumption, gestational length, or parturition.

F1 Generation	Table 101. Results for Study 01234003		
	Findings	0 mg/kg	7.5 mg/kg
	Survival PND0-PND 7	94	96
	Survival PND7-PND21	100	95
	Found dead preweaning		
	Pups (litters)	13(5)	14(8)
	Sacrificed <i>in extremis</i> preweaning	0(0)	3(2)
	Mortality postweaning	0(M)	5(M)**
		0(F)	5(F)
	Body weight (g)	23 (M)	20 (M) -13%
	PND 10	22 (F)	20 (F) -12%
	Body weight (g)	54 (M)	45 (-16%)
	PND 21	52 (F)	52 (-13%)

*The number of pups found dead in the 7.5 mg/kg/day was similar to the control group when evaluated over the entire treatment period; however, 6 (5) of these pups (litters) in the 7.5 mg/kg/day group were found dead or euthanized in extremis during PND 12–18 compared to 0 pups over this same period in the control group. Clinical observations of swollen abdominal area, swollen hindlimb, and/or pale body were observed in the pups euthanized in extremis prior to euthanasia.

**Two males and 2 females had gross findings of red matting on the surface of the skin and dark red areas on the skin associated with hemorrhage, which were the reasons for euthanasia and was associated with implantation of microchips for identification. The remaining female had gross findings of red matting and scabbing of the right ear, and red discoloration, opacity, and enlargement of the right eye; red matting of the ear and red discoloration of the eye which were the reasons for euthanasia and were associated with hemorrhage following ear tagging.

There was no apparent difference in the incidence of mortality following microchip versus ear tag identification; however, the incidence of mortality was markedly lower than in the previous Study 1234002.

Clinical signs	Table 102. Preweaning Clinical Observations (No. of Pups [No. of Litters])		
	Observation	0 mg/kg	7.5 mg/kg
	Swollen eye	0	21 (11)
	Subcutaneous hemorrhage	0	22 (11)
	Exophthalmos	0	1 (1)
	Lens opacity	0	7 (5)

Parameters	Major findings			
Body weights	Table 103. Bodyweights on PND 10 and PND 21			
	Findings	0 mg/kg	7.5 mg/kg	
	Body weight (g)	23 (M)	-13%	
	PND 10	22 (F)	-12%	
	Body weight (g)	54 (M)	-16%	
	PND 21	52 (F)	-13%	
F1 Hematology	Table 104. Hematology (% Change From Control) in Rat Pups Dosed With Oteseconazole			
	Results	PND 7	PND 21	PND 34
	RBC (x10 ⁶ cells/ μ L)	ND	-16	-5
	HGB (g/dL)	ND	-16	-8
	HCT (%)	ND	-16	-6
	RDW%	+12%	+12	+17
	WBC x10 ³ cells/ μ L	ND	-17	-27
	Reticulocytes absolute x10 ³ cells/ μ L	ND	-29	+10
	Platelets 10 ³ / μ L	+25%	+57	+28
	Lymphocytes absolute 10 ³ / μ L	ND	-25	-30
	Prothrombin time seconds	ND	+82	-4
	APTT (seconds)	ND	+141	-5
	Fibrinogen mg/dL	+25	+28	+11
	GGT (U/L)	+1088	+1255	NC (0.9) *
	Cholesterol (mg/dL)	+72	+107	+25 (M)
	Globulin (g/dL)	+30	+15	+30
	A/G (ratio)	-12	-18	-11
	Creatinine	+73	-16	-4
	K	+14	ND	ND
	Urea nitrogen	+14	+8	+16
	*% GGT change not calculated because control level was 0 but GGT level in oteseconazole treated rat at recovery was comparable to historical control values.			
	Ophthalmoscopy findings PND 21	Table 105. Ophthalmology Findings (Number of Animals Affected) on PND 21		
		Findings	0 mg/kg	7.5 mg/kg
# of pups evaluated		144	132	
Cataract		6	31	
Hyphema		1	19	
Corneal ulceration		0	4	
Corneal perforation		1	2	
Buphthalmos		0	3	
Iridial hemorrhage	0	1		
Ophthalmology findings-PND 34	Table 106. Ophthalmology Findings-Postweaning (PND 34)			
	Findings	0 mg/kg	7.5 mg/kg	
	# of pups evaluated	76	67	
	Opacity	10	20	
	Hyphema	0	7	
	Corneal ulceration	0	2	
	Buphthalmos	0	6	
Iridial hemorrhage	0	2		

Parameters	Major findings		
Necropsy findings offspring	Table 107. Summary of Gross Pathology Findings PND 21 (Non-Selected Animals)		
	Findings	0 mg/kg	7.5 mg/kg
	# of eyes evaluated	60	58
	Enlarged	0	4
	Red discoloration	0	7
	Ruptured	0	1
	Contents green	0	2
	Table 108. Summary of Gross Pathology Findings PND 33-34		
	Findings	0 mg/kg	7.5 mg/kg
	# of pups evaluated	76	67
Eye (# examined)	76	67	
Opacity	0	6	
Red contents	0	2	
Red discoloration	0	4	
Small	0	2	
Contents brown	0	1	
Contents yellow	0	1	
Optic nerve thin	0	6	
Histopathology findings	Table 109. Microscopic Findings PND 21		
	Findings	0 mg/kg	7.5 mg/kg
	Adhesion	0	2
	Retinal atrophy	0	5
	Lens degeneration	0	7
	Hemorrhage	0	8
	Optic nerve atrophy	0	1
	Hepatocellular vacuolation	3	18
	Table 110. Microscopic Findings PND 34		
	Findings	0 mg/kg	7.5 mg/kg
Adhesion	0	7	
Retinal atrophy	0	2	
Lens degeneration	0	12	
Hemorrhage	0	9	
Optic nerve atrophy	0	6	
Hepatocellular vacuolation	3	6	

Source: Reviewer generated table

Abbreviations: A/G, albumin/globulin; APTT, activated partial thromboplastin clotting time; GGT, gamma-glutamyl transpeptidase; HCT, hematocrit, HGB, hemoglobin; ND, not determined; PND, postnatal day; RBC, red blood cell, RDW, red cell distribution width; WBC, white blood cell.

Gamma-glutamyl transpeptidase (GGT) plays a key role in breaking down extracellular glutathione (GSH) and providing cysteine, the rate-limiting substrate, for intracellular *de novo* synthesis of GSH. GGT is found in high levels in the liver, kidney, pancreas, heart, and brain but elevated levels of GGT are generally interpreted to indicate damage to the liver and bile ducts. However, GGT activity is elevated in many diseases including cardiovascular disease, diabetes mellitus, and cancers. The expression of GGT is increased as an adaptive response during oxidative stress in order to facilitate GSH turnover, *de novo* GSH synthesis, and metabolism and detoxification of GSH conjugates (Zhang et al. 2005). The significance of the increased GGT levels in these pups remains unclear.

Study 01234004: An Investigative Study of the Effects of VT-1161 on Pre- and Postnatal Development in Hsd:SD and Wistar (Han) Rats

Key Study Findings

- There was a high incidence of lens opacity present in both Hsd:SD and Crl:WI(Han) rat strains at the oteseconazole dose of 7.5 mg/kg/day although there were subtle differences in the pattern of the findings.
- At PND 21, oteseconazole-related changes in both strains included altered coagulation (prolonged prothrombin time PT and APTT), hematology (mildly decreased red blood cell parameters including RBC count, hemoglobin and hematocrit, minimally decreased reticulocyte count, mildly increased platelet count, increased neutrophil count), and clinical chemistry (increased cholesterol and triglycerides and markedly increased GGT 15x and 5x in Hsd:SD and Wistar Han rats respectively).
- At PND 35, most changes had resolved but platelets and GGT remained elevated, although the values were reduced compared to Day 21 values.

Conducting laboratory location:



GLP compliance: Yes

Table 111. Methods for Study 01234004

Parameter	Method Details
Dose and frequency of dosing:	0, 7.5 mg/kg. Daily.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% Carboxymethylcellulose (CMC, medium viscosity) in deionized water
Species/strain:	<i>Rattus norvegicus</i> , Crl:WI(Han) and Hsd:SD
Number/sex/group:	16 pregnant females/group
Satellite groups:	None
Study design:	Oteseconazole or vehicle were administered to the F0 females by a daily oral gavage dose from Gestation Day 6 through Lactation Day 20. Records were kept of viability, clinical observations, body weights, food consumption and parturition in dams. Records were kept of viability, clinical observations, sex, body weights, ophthalmic examinations, clinical pathology, hematology, coagulation, serum chemistry. On postnatal day 35 or 36 all pups were euthanized. Each pup was subjected to a complete necropsy exam and gross lesions were collected. The eyes and optic nerves were preserved in Davidson solution for any animals with ophthalmic exam observations.
Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer generated table

Table 112. Observations and Results for Study 01234004

Parameters	Major Findings																									
F1 Survival	Table 113. Postnatal Survival %																									
	<table border="1"> <thead> <tr> <th>Findings</th> <th colspan="2">Hsd:SD</th> <th colspan="2">Cri:WI(Han)</th> </tr> </thead> <tbody> <tr> <td>Oteseconazole dose (mg/kg)</td> <td>0</td> <td>7.5</td> <td>0</td> <td>7.5</td> </tr> <tr> <td>Pup survival to PND 4 (%)</td> <td>87</td> <td>91</td> <td>85</td> <td>94</td> </tr> <tr> <td>Pup survival PND 4 to PND21 (%)</td> <td>98</td> <td>94</td> <td>99</td> <td>96</td> </tr> </tbody> </table> Source: Reviewer generated table	Findings	Hsd:SD		Cri:WI(Han)		Oteseconazole dose (mg/kg)	0	7.5	0	7.5	Pup survival to PND 4 (%)	87	91	85	94	Pup survival PND 4 to PND21 (%)	98	94	99	96					
Findings	Hsd:SD		Cri:WI(Han)																							
Oteseconazole dose (mg/kg)	0	7.5	0	7.5																						
Pup survival to PND 4 (%)	87	91	85	94																						
Pup survival PND 4 to PND21 (%)	98	94	99	96																						
Clinical signs	Clinical observations in Hsd:SD and HAN rats included tremors (19 and 2 pups, respectively) and swollen abdominal area, (76 and 46 pups, respectively). Only Hsd:SD rats showed small stature (16 pups), subcutaneous hemorrhage of the ventral trunk (16 pups), facial area (2 pups), and/or dorsal head (1 pup) and pale eyes (3 pups).																									
Body weights	Table 114. Body Weights in F1 Pups																									
	<table border="1"> <thead> <tr> <th>Findings</th> <th colspan="2">Hsd:SD</th> <th colspan="2">Cri:WI(Han)</th> </tr> </thead> <tbody> <tr> <td>Oteseconazole dose (mg/kg)</td> <td>0</td> <td>7.5</td> <td>0</td> <td>7.5</td> </tr> <tr> <td>Pup body weight PND 4</td> <td>49</td> <td>-22%</td> <td>45</td> <td>-7%</td> </tr> <tr> <td>Pup body weight PND 21</td> <td>83</td> <td>-13%</td> <td>81</td> <td>-6%</td> </tr> <tr> <td>Pup body weight PND 34</td> <td>133</td> <td>-11%</td> <td>130</td> <td>-4%</td> </tr> </tbody> </table> Source: Reviewer generated table	Findings	Hsd:SD		Cri:WI(Han)		Oteseconazole dose (mg/kg)	0	7.5	0	7.5	Pup body weight PND 4	49	-22%	45	-7%	Pup body weight PND 21	83	-13%	81	-6%	Pup body weight PND 34	133	-11%	130	-4%
Findings	Hsd:SD		Cri:WI(Han)																							
Oteseconazole dose (mg/kg)	0	7.5	0	7.5																						
Pup body weight PND 4	49	-22%	45	-7%																						
Pup body weight PND 21	83	-13%	81	-6%																						
Pup body weight PND 34	133	-11%	130	-4%																						

APPEARS THIS WAY ON ORIGINAL

Parameters	Major Findings				
F1 Generation	Table 115. Oteseconazole-Related Increase in Lens Opacity in Hsd:SD and Crl:WI(Han) Rat				
	Incidence of Lens Opacity (Cataracts)				
	Oteseconazole dose	0		7.5 mg/kg	
	Rat strain	Hsd:SD	Crl:WI (Han)	Hsd:SD	
				Crl:WI (Han)	
	Preweaning: PND 17-22	1/55	0/48	11/65	32/61
	Postweaning: PND 30-36	7/55	0/48	30/62	27/61

Source: Reviewer generated table

Table 116. Oteseconazole-Related Hematology, Coagulation and Clinical Chemistry Findings

Findings	Hsd:SD		Crl:WI(Han)	
	0	7.5	0	7.5
RBC				
PND 21	4.6	3.9* (-15%)	4.8	4.4* (-7%)
PND 35	6.6	6.4 (-3%)	6.7	6.6 (-2%)
HGB				
PND 21	8.2	6.1* (-26%)	8.4	6.9* (-18%)
PND 35	13.2	12.9 (-2%)	12.7	12.5 (-2%)
HCT				
PND 21	29	21* (-28%)	27	23* (-15%)
PND 35	43	43 (-0%)	43	42 (-2%)
Reticulocytes				
PND 21	1111	833* (-25%)	872	754 (-14%)
PND 35	696	841 (+20%)	720	786 (+9%)
MCV				
PND 21	62	53* (-16%)	57	52* (-9%)
PND 35	67	69 (+3%)	64	64 (-0%)
MCH				
PND 21	18	16* (-12%)	18	16* (-12%)
PND 35	20	20 (-0%)	19	19 (-0%)
RDW				
PND 21	25	27 (+8%)	24	26 (+8%)
PND 35	17	20 (+18%)	17	20 (+18%)
Platelets				
PND 21	1147	1996* (+74%)	980	1799* (+83%)
PND 35	1086	1371* (+26%)	935	1170* (+25%)
Neutrophils				
PND 21	0.36	0.65 (+80%)	0.50	0.62 (+24%)
PND 35	0.55	0.56 (+2%)	0.56	0.43 (-23%)
Prothrombin time				
PND 21	14	21* (+50%)	15.1	16.5* (+9%)
PND 35	16	16 (+0%)	16.3	15.4 (-6%)
APTT (seconds)				
PND 21	9.4	20* (+120%)	8.0	13.9* (+73%)
PND 35	12.6	12.4 (-2%)	11.2	10.5 (-6%)
GGT				
PND 21	2.6	38* (+1360%)	2.5	11.3* (+352%)
PND 35	0.4	3.4* (+750%)	0.3	2.2* (+633%)
ALP				
PND 21	735	472* (-36%)	407	324 (-20%)
PND 35	403	351 (-13%)	335	289 (-14%)

Parameters	Major Findings			
Cholesterol				
PND 21	142	270* (+90%)	130	216* (+66%)
PND 35	99	107 (+8%)	75	77 (+3%)
Triglycerides				
PND 21	117	236* (+102%)	190	144 (-24%)
PND 35	44	43 (-2%)	59	59 (-0%)
Albumin				
PND 21	3.3	3.1* (-6%)	3.3	3.1 (-6%)
PND 35	3.6	3.6 (-0%)	3.7	3.7 (-0%)
Globulin				
PND 21	1.3	1.4* (+8%)	1.2	1.3* (+8%)
PND 35	1.5	1.5 (+0%)	1.5	1.5 (+0%)
A/G ratio				
PND 21	2.6	2.2* (-15%)	2.6	2.3* (-12%)
PND 35	2.4	2.4 (-0%)	2.5	2.4 (-4%)

*statistically significant difference compared to control

Necropsy findings	Hsd:SD Opacity in two animals
Offspring	CrI:WI(Han) Enlarged eye

Source: Reviewer generated table

Abbreviations: A/G, albumin/globulin; APTT, activated partial thromboplastin clotting time; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; HCT, hematocrit, HGB, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PND, postnatal day; RBC, red blood cell; RDW, red cell distribution width

Specifications for Impurities/Degradants

The limit for each individual related product was set at $\leq 0.2\%$, consistent with International Conference on Harmonisation (ICH) Q3B(R2) based upon a maximum daily dose of 600 mg. All individual impurities have been detected at less than (b) (4) %.

All potential and actual impurities in oteseconazole with origins in the final manufacturing steps were classified according to ICH M7(R1) using in-silico methods unless otherwise noted, with some undergoing Ames testing. Most were classified as Class 5 but three were designated as Class 4 because the updated software (Derek 6.0.0 Nexus 2.2.0 (mutagenicity only) and Leadscope Model Applier version 2.3.7-1 (mutagenicity suite)) provided an alert for the trifluoroethoxy portion. Since the trifluoroethoxy portion is also contained in oteseconazole, which is negative in the Ames assay and earlier versions of the software did not provide alerts for this subunit, compounds with this structural feature were designated as class 5.

Table 117. Batch Analyses for GMP Batches of Oteseconazole Manufactured by (b) (4)

Test	Limit (Proposed Commercial Acceptance Criteria)	884W1S001M	884W1S002M	884W1S003M	884W1S004M	884E1S0003M
Appearance	White to off-white solid	White solid	White solid	White solid	White solid	White solid
Identification	Conforms to reference spectrum	complies	complies	complies	complies	complies
	(b) (4) % of the average retention time of the standard	complies	complies	complies	complies	complies
Assay (wt/wt %)	(b) (4)					
Related Substances						
(b) (4)						

Source: Part of Applicant's Table 46 from NDA 215888 Section 3.2.S.3.2 Impurities.
 Abbreviations: AUC, area under the curve; GMP, good manufacturing practice; NMT, not more than; wt, weight.

One (b) (4) weak carcinogen in female mice, which will be controlled (b) (4) with a limit of NMT (b) (4) ppm. This is acceptable based on ICH M7 guidelines. Impurity (b) (4) (b) (4) will be controlled at NMT (b) (4)%. (b) (4) This is acceptable. (b) (4) (b) (4) impurity are nongenotoxic and will be controlled (b) (4) with limits of NMT (b) (4)%. (b) (4) is controlled with a limit of NMT (b) (4)% in oteseconazole.

(b) (4)

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

14.1.1. Plasma Protein Binding (MC11M-0008.1 and OPR-VMT-0449.01)

Study MC11M-0008.1 evaluated the extent of oteseconazole binding to mouse, rat, dog and human plasma proteins at concentrations of 0.26, 2.5, 26 and 105 µg/mL using equilibrium dialysis. Oteseconazole was observed to bind extensively to plasma proteins, with percentage bound of 99.5±0.058 and 99.7±0.058 in human plasma at concentrations of 0.26 and 2.5 µg/mL, respectively. The degree of protein binding decreased slightly to 98.2±1.07 and 98.5±0.35 at concentrations of 26 and 105 µg/mL, respectively, likely indicating saturation of binding to plasma proteins. Study OPR-VMT-0449.01 was a comparative assessment of plasma protein binding in human plasma for oteseconazole and 4 other antifungal agents (i.e., itraconazole, posaconazole, fluconazole and terbinafine) at a concentration of 5µM. Consistent with Study MC11M-0008.1, oteseconazole plasma protein binding was determined to be 99.8% at this concentration (which is equivalent to 2.64 µg/mL).

Reviewer's Comment: The range of C_{max} values associated with the proposed dosing regimen is 1.4 – 2.8 µg/mL. Therefore, the clinically relevant range of protein binding values for oteseconazole is 99.5 - 99.7%.

Drug-Drug Interactions

Cytochrome P450 Enzymes

In vitro studies indicated that oteseconazole is stable under the incubation conditions evaluated; little to no loss was observed in the incubations with human liver microsomes and minimal loss (< 18%) was observed when incubated with various recombinant human cytochrome (CYP) P450 isoenzymes (i.e., CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). C1 (hydroxylation and glucuronide conjugation) was only formed by dog hepatocytes and no additional metabolites were formed by Sprague Dawley (SD) rat, Cynomolgus monkey and human hepatocyte.

Reviewer's Comments: The reviewer agrees that no clinical DDI studies using strong index inhibitors and/or inducers of CYP enzymes are needed. Based on the above findings and absorption, distribution, metabolism, excretion (ADME) study results [where no metabolites were identified in pooled plasma samples], metabolism is not expected to contribute significantly to the elimination of oteseconazole.

In vitro evaluation of oteseconazole as an inhibitor of CYP450 enzymes involved incubation of oteseconazole at concentrations ranging from 0.01 to 10 µM in pooled human liver microsomes with metabolic substrates at their determined K_m concentrations. Following a 5-minute incubation, reactions were quenched with acetonitrile and substrate metabolites were analyzed by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Study results indicate that

oteseconazole is a direct, reversible inhibitor of several CYP isoforms in the following order of decreasing inhibitory potency: CYP2C8 ($IC_{50} = 1.4 \mu\text{M}$) > CYP2B6 ($IC_{50} = 4.0 \mu\text{M}$) > CYP2C19 ($IC_{50} = 9.7 \mu\text{M}$), CYP2D6 ($IC_{50} = 9.4 \mu\text{M}$), CYP3A (as measured by testosterone 6 β -hydroxylation, $IC_{50} = 9.6 \mu\text{M}$) > CYP2C9 ($IC_{50} > 10 \mu\text{M}$), CYP3A (as measured by midazolam 1'-hydroxylation, $IC_{50} > 10 \mu\text{M}$). Oteseconazole did not inhibit CYP1A2 within the range of concentrations evaluated. Additionally, oteseconazole showed little to no time- or metabolism-dependent inhibition of any of the tested CYP isoforms.

Reviewer's Comments: *In the inhibition study, 10 μM of oteseconazole was the upper end of the concentration range evaluated due to solubility limitations.*

Although the activities of CYP2C9 and CYP3A (with midazolam as the substrate) were reduced by approximately 48% and 42%, respectively, IC_{50} values for CYP3A and CYP2C9 reported as $>10 \mu\text{M}$.

The ability of oteseconazole to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 enzymes was evaluated in vitro in primary cultures of cryopreserved human hepatocytes. Induction was assessed by measuring activity and expression of the CYP enzymes after treatment with oteseconazole (10 μM). The study results indicate that treatment with up to 10 μM oteseconazole caused increases (> 2 -fold change and/or $> 20\%$ of the positive control) in CYP1A2, CYP2B6 and CYP3A4/5 activity and CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mRNA levels in at least 2 hepatocyte cultures.

Reviewer's Comments: *In summary, based on in vitro study results, oteseconazole has shown both inhibition and induction potential for all tested CYP enzymes, except for CYP1A2. Oteseconazole showed only induction effect on CYP1A2.*

Following completion of these studies, the Applicant assessed the clinical relevance of the in vitro CYP inhibition and induction data by comparing the inhibition/induction potency to steady-state plasma concentrations of oteseconazole achieved in humans at clinically relevant doses. The first step was a basic analysis that considered only the in vitro inhibitory or induction potency and the highest anticipated C_{max} in humans, based on total drug (protein bound + unbound) in plasma at steady state. If the analysis suggested that a drug-drug interaction (DDI) may possibly occur in vivo, a second analysis utilizing a mechanistic static model was then performed.

Based on the basic, step 1 analysis for evaluation of CYP inhibition potential, a DDI study would be recommended for each of the CYP isoforms evaluated in the CYP inhibition study except for CYP1A2. Based on the basic, step 1 analysis for evaluation of CYP induction potential, a DDI study would be recommended for each of the isoforms tested.

Reviewer's Comments: *Per the FDA guidance for industry In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020), the recommended equation for the calculation of the RI value for basic model of reversible inhibition is $RI = 1 + (I_{\text{max}}, u/K_i, u)$, where I_{max}, u is the maximal unbound plasma concentration of the interacting drug at steady state, and K_i, u is the unbound inhibition constant determined in vitro. For Step 1, the basic model analysis, the Applicant used the formula $R_1 = 1 + [I]/K_i$, where $[I]$ is the maximum total concentration (protein bound + unbound) of the inhibitor in plasma at steady state in humans receiving a therapeutic dose of the drug; and K_i is*

the inhibition constant of the inhibitor for the CYP isoform in question. Also, the guidance recommends 1.02 for the cutoff value (R1), however, the Applicant used the cutoff value of 1.1 for R1. Additionally, the formula used for basic model analysis for CYP induction is also slightly different from the guidance, which is $R_3 = 1 / \{1 + (d \cdot E_{max} \cdot [I]) / (EC_{50} + [I])\}$, while the formula in the guidance is $R_3 = 1 / [1 + d \times ((E_{max} \times 10 \times I_{max,u}) / (EC_{50} + 10 \times I_{max,u}))]$. The cutoff for R3 used by Applicant is 0.9 whereas the guidance recommends cutoff value of R3 is 0.8. Although the validity of the Applicant's approach cannot be verified, the Applicant's conclusions suggest a worst-case scenario of a potential for clinically relevant DDIs with all CYP isoforms. Therefore, from a risk assessment perspective, the reviewer agrees with the Applicant's decision to further evaluate the need for clinical DDI studies.

To further evaluate the need for clinical DDI studies, refine these decisions, a step 2 analysis was performed by the Applicant using a mechanistic static model, which predicts the in vivo area under the curve ratio (AUCR). If AUCR is > 1.25, this indicates net inhibition and if AUCR is < 0.8, this indicates net induction. If either of these conditions are met, an in vivo human DDI study is recommended. The results are shown in [Table 118](#) below. The study results suggest that all AUCR values are within the range of 0.8 and 1.25, and thus there is no recommendation to perform a CYP based DDI study in humans.

Table 118. Mechanistic Static Assessment of the Need to Conduct an In Vivo Human DDI Study – CYP Inhibition + Induction

CYP Isoform	IC ₅₀ (µM)	Ki (µM) ^a	Model Substrate	AUCR	In Vitro DDI (AUCR>1.25 or <0.8)?
1A2	10.00	5.00	Theophylline	0.98	No
	10.00	5.00	Clozapine	0.98	No
	10.00	5.00	Caffeine	0.98	No
2B6	4.00	2.00	Bupropion	0.98	No
2C8	1.40	0.70	Montelukast	1.01	No
	1.40	0.70	Pioglitazone	1.01	No
	1.40	0.70	Repaglinide	1.01	No
	1.40	0.70	Rosiglitazone	1.01	No
2C9	10.00	5.00	Tolbutamide	1.00	No
	10.00	5.00	S-warfarin	1.00	No
	10.0	5.00	Rac-warfarin	1.00	No
2C19	9.70	4.85	S-mephenytoin	1.00	No
	9.70	4.85	Omeprazole	1.00	No
2D6	9.40	4.70	Desipramine	1.00	No
	9.40	4.70	Metoprolol	1.00	No
	9.40	4.70	Dextromethorphan	1.01	No
3A4 (M)	10.0	5.00	Midazolam	1.07	No
	10.0	5.00	Triazolam	1.06	No
	10.0	5.00	Alprazolam	0.99	No
	10.0	5.00	Buspirone	1.15	No
	10.0	5.00	Simvastatin	1.05	No
	10.0	5.00	Nifedipine	1.04	No

CYP Isoform	IC ₅₀ (μ M)	Ki (μ M) ^a	Model Substrate	AUCR	In Vitro DDI (AUCR>1.25 or <0.8)?
3A4(T)	9.60	4.80	Midazolam	1.08	No
	9.60	4.80	Triazolam	1.07	No
	9.60	4.80	Alprazolam	1.00	No
	9.60	4.80	Buspirone	1.18	No
	9.60	4.80	Simvastatin	1.06	No
	9.60	4.80	Nifedipine	1.05	No

Source: Summarized from Applicant's ISR VMT-CYP-003

Ki is estimated as IC₅₀/2 as determined at substrate concentration near their Km values

Abbreviations: AUCR, area under the curve ratio; CYP, cytochrome P450; DDI, drug-drug interaction; IC₅₀, concentration inhibiting 50% activity; Ki, inhibition constant.

Reviewer's Comments: *Per the FDA in vitro DDI guidance, "in addition to the combination of inhibition and induction, one should separately use inhibition mechanisms (A and B only) to predict a drug's enzyme inhibition potential (i.e., assuming C is equal to 1), and use induction mechanisms (C only) to predict a drug's enzyme induction potential (i.e., assuming A and B are equal to 1). It should be noted that concurrent prediction may lead to a false negative prediction if the inhibition potential is over-predicted, thus masking the induction effect. If the induction potential is over-predicted, it will mask the inhibition effect."*

In the study report VMT-CYP-001, the Applicant conducted a mechanistic static assessment of the need to conduct a clinical DDI study using only CYP inhibition data. The analysis results indicate that the risk of a significant CYP inhibition based DDI is low for all the isoforms evaluated except CYP3A4/5. The Applicant did not conduct induction mechanistic static assessment by using CYP induction data only. Instead, after CYP inhibition mechanism assessment, the Applicant directly combined induction parameters in the inhibition assessment and concluded that a lack of significant AUCR values across all isoforms. Without a prediction of induction effect only, concurrent prediction may mask the induction effect if the inhibition potential is over-predicted. However, the Applicant's assessment is considered acceptable based on following reasons.

- *When only CYP inhibition data were considered in the mechanistic static model analysis, the only isoform that was indicated as being potentially at risk for a clinically relevant drug interaction was CYP3A. Therefore, besides CYP3A inhibition, it is unlikely that inhibition of the other CYP isoforms are over-predicted.*
- *With regards to CYP3A4, a clinical drug interaction study for CYP3A4 was conducted by the Applicant using midazolam as the substrate. The study results demonstrated that oteseconazole is a weak inducer of CYP3A4. For further information, please see the clinical DDI section in this review.*

At the End of Phase II Meeting the FDA raised the following concern: "Based on in vitro studies, there is a potential for DDI [drug-drug interactions] between VT-1161 and CYP2C8 substrates. Therefore, we recommend that you exclude subjects taking sensitive CYP2C8 substrates (e.g., repaglinide) from the trials." The FDA also stated the mechanistic static model requires assumptions that may not always be accurate and requested Viamet to provide clarification about the assumptions used in mechanistic static model calculations. To address the concern raised by the FDA, updated mechanistic static calculations for CYP2C8 were performed in study report VMT-CYP-003. The results of the updated mechanistic static model calculations

showed that calculated AUCR values did not fall outside of the 0.8 to 1.25 window for any CYP2C8 model substrate evaluated under any of the updated scenarios. The four scenarios assessed by the Applicant are as follows: Scenario 1 represents the updated base-case scenario for oteseconazole in the treatment of RVVC (150-mg dose). Scenario 2 represents lower protein binding than the base-case scenario. Scenario 3 represents higher $[I]_{max,b}$ values than the base-case scenario. Scenario 4 represents a worst-case scenario with a combination of lower protein binding and higher $[I]_{max,b}$ values than the base-case scenario.

Transporters

Bidirectional permeability studies were conducted by the Applicant to evaluate whether oteseconazole is a substrate of P-gp and BCRP. The study results showed that in the presence of bovine serum albumin (BSA), the efflux ratio of oteseconazole was below 2 in both the presence and absence of the P-gp inhibitor, valsopodar, suggesting that oteseconazole is not a substrate of P-gp. The efflux ratio of oteseconazole in MDCKII-BCRP cells was below 2 in the presence and absence of a BCRP inhibitor, Ko143, suggesting that oteseconazole is not a substrate of BCRP.

To determine if oteseconazole is a substrate of human uptake transporters such as organic anion transporting polypeptides (OATP)1B1, OATP1B3, organic cation transporter (OCT)2, OAT1 and OAT3, the accumulation of oteseconazole in transporter-expressing and control HEK293 cells was measured. The accumulation of oteseconazole in OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 expressing cells was not reduced in the presence of positive control inhibitors. The results suggest that oteseconazole is not a substrate of OATP1B1, OATP1B3, OCT2, OAT1 and OAT3.

In vitro inhibition study results showed that oteseconazole inhibited P-gp with calculated IC_{50} values of 2.88 μ M and inhibited BCRP with IC_{50} values of 0.415 μ M, respectively. Oteseconazole inhibited OATP1B1 and OATP1B3 with calculated IC_{50} values of 2.97 and 2.57 μ M, respectively. Oteseconazole (2.5 and 25 μ M) did not inhibit OCT2, OAT1 or OAT3.

Reviewer's Comments: *In the clinical pharmacology summary, the Applicant mentioned that "the clinical relevance of in vitro inhibition of human transporters P-gp and BCRP was evaluated based on the analyses recommended by the FDA in the study report of VMT-CYP-002. The systemic efflux transporter assessment using the unbound C_{max} for oteseconazole suggested that there was a risk of clinically relevant inhibition of BCRP, but not P-gp or OATP1B1/1B3". However, the study report VMT-CYP-002 was not submitted by the Applicant. Based on the FDA's In Vitro DDI guidance, $R=1+((f_{u,p} \times I_{in,max})/IC_{50})$ with cutoff value of 1.1 is used to determine whether the investigational drug has the potential to inhibit OATP1B1/3. The reviewer calculated R values (based on $f_{u,p} = 0.5\%$, $I_{in,max} = 10\mu$ M, and $MW=527.39$ g/mol), for OATP1B1 and OATP1B3 are 1.03 and 1.04, respectively, which is less than the cutoff value of 1.1. Therefore, the results are in line with the Applicant's assessment. The oteseconazole concentration of 10 μ M used for [I] is the concentration used in the in vitro transporter inhibition study, which is higher than mean C_{max} shown in the clinical studies and presents the worst-case scenario.*

In addition, the Applicant has conducted clinical DDI studies with P-gp and BCRP substrates (Study VMT-VT-1161-CL-015). For detailed information, please see the clinical DDI section in this review.

Summary

Given that the Applicant did not conduct any in vitro studies to evaluate whether oteseconazole is a substrate or an inhibitor of (multidrug and toxic compound extrusion) MATE transporter in the original submission, an information request (IR) request was sent to the Applicant for clarification on 08/04/2021. However, the clarifications provided in the IR response dated 08/12/2021 were inadequate. Based on subsequent communication with the Applicant, the Applicant agreed to conduct in vitro MATE substrate and inhibitor interaction study in the post-marketing setting, if the NDA is approved.

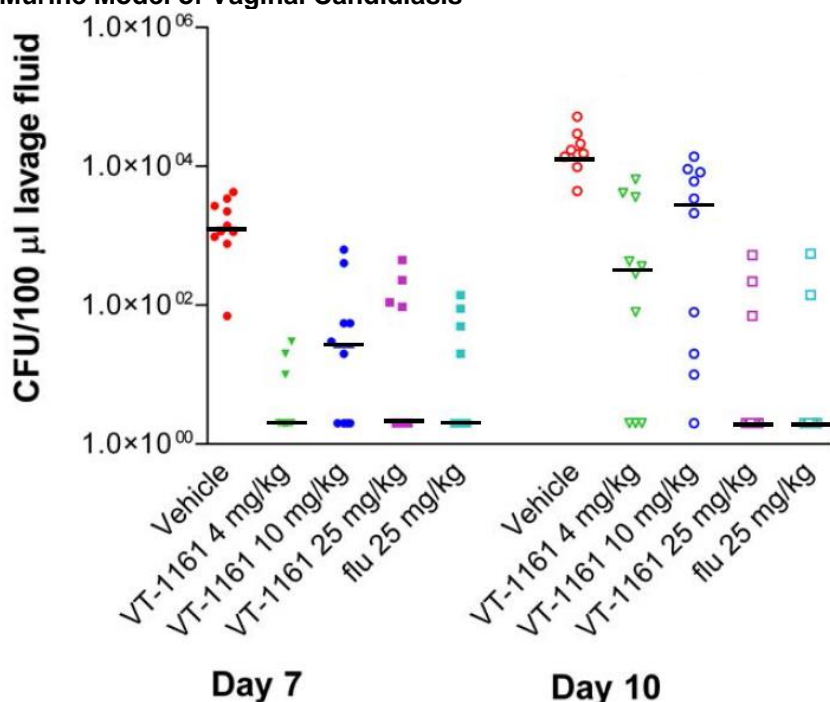
14.2. In Vivo Studies

14.2.1. In Vivo Activity in an Estrogen-Dependent Murine Model of Vaginal Candidiasis

Study VMT-LSU-1 evaluated the antifungal activity of 4, 10, and 25 mg/kg doses of oteseconazole in mice vaginally infected with *C. albicans*. To maintain a persistent vaginal candida infection, female CBA/J mice (N=10/treatment group) were administered 0.1 mg SC estradiol 3 days prior to and 4 days following vaginal inoculation with a wild-type strain of *C. albicans*. Vehicle treated mice served as a negative control while mice treated with a 25 mg/kg dose of fluconazole served as the positive control. Beginning 3 days post-inoculation, treatments were administered once daily via oral gavage for 3 days. At the end of treatment, the vaginal cavity lavage fluid was collected on Study Day 7 (i.e., 1 day after the end of treatment) and Day 10 for enumeration of vaginal fungal burden. Blood and vaginal tissue were also collected on Study Day 10 for assessment of plasma and vaginal tissue drug concentrations. Drug concentrations were quantified using a validated LC-MS/MS method.

Compared to vehicle-treated mice, oteseconazole-treated mice exhibited a statistically significantly lower fungal burden at both Days 7 and 10 (p value ≤ 0.0002). There was no apparent dose-response at Day 7 as all dose levels achieved median reductions in fungal burden of >90% compared to vehicle. However, at Day 10, regrowth was observed at all but the 25 mg/kg dose level. Additionally, the 25 mg/kg dose of oteseconazole maintained the same degree of antifungal activity as the 25 mg/kg fluconazole dose at both Days 7 and 10 ([Figure 7](#)). Plasma and vaginal tissue drug concentrations were generally comparable, as summarized in [Table 119](#).

Figure 7. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis



Source: Figure 1 of Applicant's ISR VMT-LSU-1
 Abbreviations: CFU, colony forming units

Table 119. Oteseconazole Drug Concentrations ± SD in Plasma and Vaginal Tissue

Oteseconazole Dose (mg/kg)	Plasma Concentration (µg/mL)	Vaginal Tissue Concentration (µg/mL)
4	0.84 ± 0.16	1.53 ± 0.32
10	4.01 ± 1.32	5.80 ± 1.05
25	11.60 ± 3.69	15.82 ± 3.16

Source: Summarized from Table 3 of Applicant's ISR VMT-LSU-1

Study VMT-LSU-2 was conducted as a follow-up to Study VMT-LSU-1 to evaluate the antifungal activity of 25 mg/kg dose of oteseconazole against a panel of clinical isolates resistant to fluconazole in the murine model of vaginal candidiasis. Similar to the preceding study, female CBA/J mice were rendered pseudo-estrus prior to vaginal inoculation, and treatment was initiated 3 days post-inoculation through Study Day 6. Vaginal lavage fluid and blood were collected as described for Study VMT-LSU-1 for quantitation of fungal burden and drug concentrations. Following initial feasibility studies, clinical isolates (fluconazole and oteseconazole MICs summarized in [Table 120](#)) were selected to evaluate the in vivo activity of oteseconazole. For most comparisons, oteseconazole was found to be statistically superior to vehicle and fluconazole in reducing fungal burden for isolates AR466-06 and JJ300-06. Results of a repeat experiment for isolate AR466-06 ([Figure 8](#), left) were consistent with the original observations. For isolate LP1158-07, which had a higher oteseconazole minimum inhibitory concentration (MIC), the activity of oteseconazole was diminished, and appeared comparable to vehicle and fluconazole. Statistical analysis of the median CFU data is summarized in [Table 121](#) for all 3 isolates. For isolate AR466-06, statistical analysis is shown for the first experiment only.

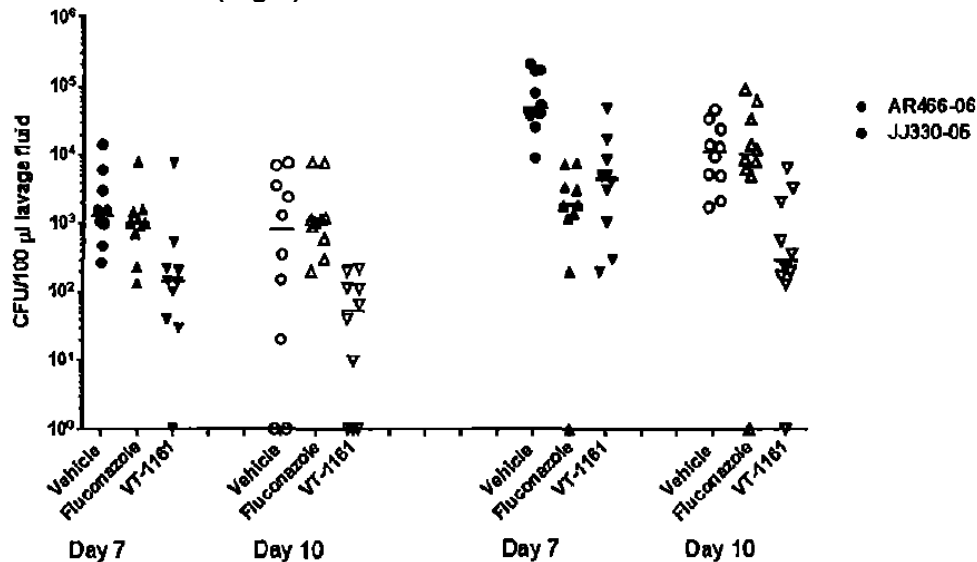
Table 120. Fluconazole and Oteseconazole MICs for Clinical Isolates Used in Study VMT-LSU-2

Isolate	Fluconazole MIC ($\mu\text{g/mL}$)	Oteseconazole MIC ($\mu\text{g/mL}$)
AR466-06	64	≤ 0.015
JJ330-06	8	0.12
LP1158-07	64	2

Source: Summarized from Table 1 of Applicant's ISR VMT-LSU-2
 Abbreviations: MIC, minimum inhibitory concentration.

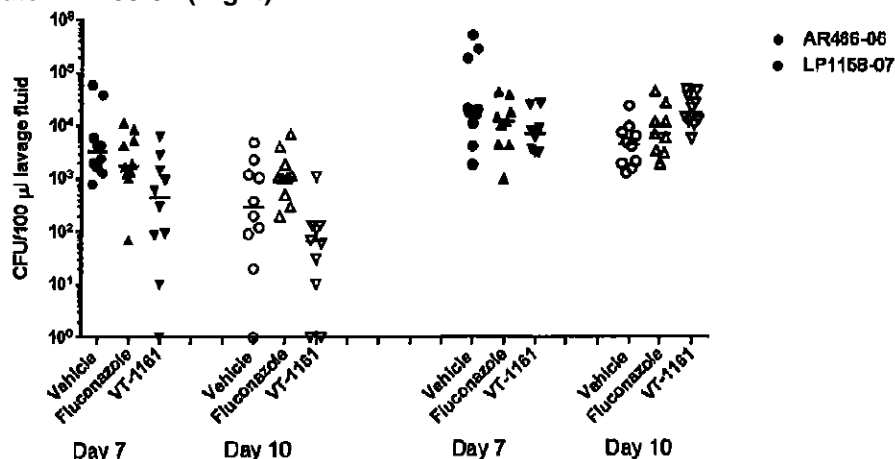
Reviewer's Comment: The oteseconazole MICs for *C. albicans* reported in Phase 3 trials ranged from ≤ 0.0005 to $> 0.25 \mu\text{g/mL}$. Thus, the range of MICs used in nonclinical studies generally overlaps with the range observed for the Phase 3 trials. The MIC90 from these trials were: 0.008, 0.03 and 0.06 $\mu\text{g/mL}$ for studies CL-11, CL-12 and CL-17, respectively. Consistent with observations from the nonclinical studies, there was a general trend towards reduced mycologic eradication with increasing MIC for the Phase 3 *C. albicans* isolates.

Figure 8. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis Following Inoculation With Isolate AR466-06 (Left) and Isolate JJ330-06 (Right)



Source: Figure 2 of Applicant's ISR VMT-LSU-2
 Abbreviations: CFU, colony forming units.

Figure 9. Vaginal CFU Measured on Days 7 (1 Day Post-Treatment) and 10 (4 Days Post-Treatment) in a Murine Model of Vaginal Candidiasis Following Inoculation With Isolate AR466-06 (Left) and Isolate LP1158-07 (Right)



Source: Figure 3 of Applicant's ISR VMT-LSU-2
 Abbreviations: CFU, colony forming units.

Table 121. Statistical Analyses of Mean CFU Data (P-values Based on Mann-Whitney U Test)

Variables	AR466-06		JJ330-06		LP1158-07	
	Day 7	Day 10	Day 7	Day 10	Day 7	Day 10
Oteseconazole versus vehicle	0.002	0.06	0.0003	0.0005	0.085	0.001
Oteseconazole versus fluconazole	0.006	<0.001	0.24	0.002	0.31	0.06

Source: Summarized from Figures 2 and 3 of Applicant's ISR VMT-LSU-2
 Abbreviations: CFU, colony forming units.

14.2.1.1. Human PK Studies in Healthy Volunteers

Single Ascending Dose

Study VMT-VT-1161-CL-001 was a single ascending dose study to characterize the PK, safety and tolerability of oteseconazole in 64 healthy adult subjects. This study also featured an exploratory objective to evaluate the effect of high-fat food on the bioavailability of oteseconazole. Subjects were enrolled sequentially to 6 cohorts with 8 subjects per cohort, and randomly allocated 3:1 to receive either oteseconazole (at doses of 5, 10, 20, 40, 80 or 160 mg) or placebo under fasted conditions (defined as an overnight fast of at least 10 h with continued fasting for 4 h post-dosing). Food effect was evaluated in two additional cohorts (7 and 8), where subjects received 320 mg oteseconazole under fasted conditions or 30 min after a high-fat meal (defined as ~900 kcal total; 50% fat), respectively.

Blood sampling for PK assessment was conducted pre-dose and at pre-specified times through 72 h post-dosing during a 4-day confinement period. Thereafter, outpatient PK blood samples were obtained on Days 7 and 14 for Cohorts 1-6, and on Days 28 and 42 for Cohorts 7 and 8. Plasma PK samples were analyzed using a validated LC-MS/MS method. Pharmacokinetic assessments included: C_{max} , time to maximum concentration (T_{max}), the area under the curve from zero to infinity ($AUC_{0-\infty}$), apparent volume of distribution during terminal phase (V_z/F), apparent clearance (CL/F), and half-life ($t_{1/2}$).

Sixty of the sixty-four enrolled subjects completed the study. Oteseconazole was well tolerated and no study discontinuations were attributed to treatment-emergent adverse events (TEAEs); all

4 subjects who failed to complete the study were lost to follow-up. The PK population was comprised of subjects with a sufficient number of concentration-time data to provide a PK profile for noncompartmental analysis. Because most of the plasma oteseconazole concentrations were below the lower limit of quantification (LLOQ) of 20.0 ng/mL for subjects who received a dose of 5 mg or 10 mg, data from these cohorts were excluded from the PK summary statistics presented in [Table 122](#). Plasma concentration-time profiles for dose levels of 20 – 320 mg are shown in [Figure 10](#).

Table 122. Mean (±SD) PK Parameters for Oteseconazole in PK Population

Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-inf} (h·ng/mL)	CL/F (L/h)	V _z /F (L)	t _{1/2} (h)
20	44.7 (13.2)	5.01 (1.08)	16145 (6339)	1.39 (0.49)	696 (123)	393 (166)
40	79.7 (26.4)	9.67 (2.34)	35037 (15137)	1.30 (0.51)	939 (228)	548 (183)
80	165 (51.2)	4.67 (1.03)	84635 (35187)	1.08 (0.41)	761 (181)	536 (220)
160	180 (49.0)	5.67 (2.66)	108869 (36981)	1.67 (0.73)	1397 (415)	618 (169)
320 (fasted)	338 (101)	5.67 (2.34)	241971 (35056)	1.35 (0.25)	1649 (349)	873 (261)
320 (fed)	988 (305)	6.68 (2.09)	953119 (501688)	0.41 (0.17)	741 (129)	1467 (641)

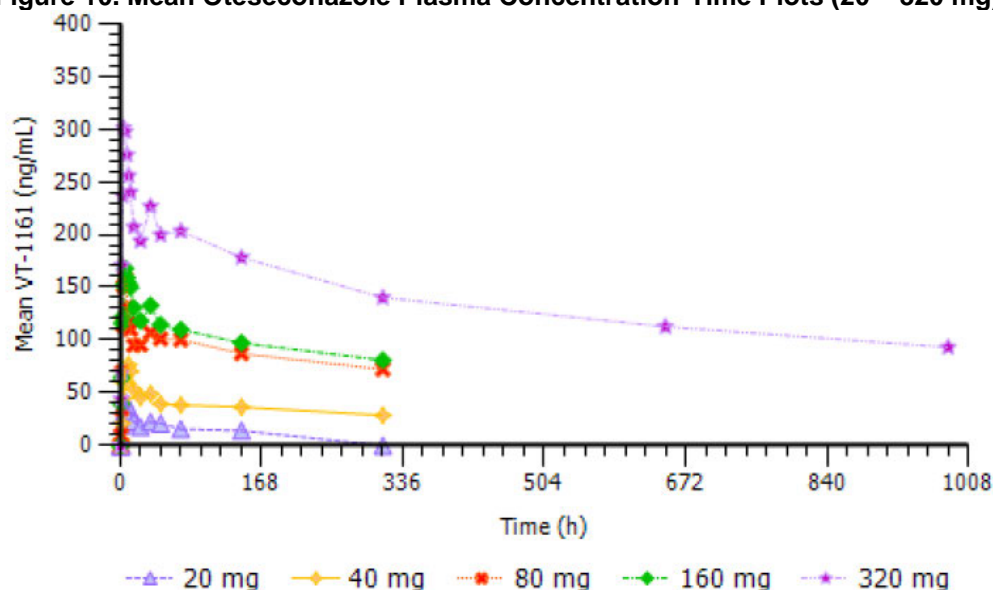
Source: Summarized from Table 11-3 of Applicant's ISR VMT-VT-1161-CL-001

N = 6 for all PK parameters except at the 20-mg dose, where N = 6 for C_{max} and T_{max}, and N = 5 for other parameters.

Abbreviations: AUC_{0-inf}, area under the curve from zero to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; t_{1/2}, half-life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution during terminal phase.

Reviewer's Comment: *Of note, the oteseconazole formulation used in this study was a (b) (4) capsule subject to a more pronounced food effect than the Phase 3 (b) (4) capsule formulation (see Study VMT-VT-1161-CL-013). The elimination half-life summarized in [Table 122](#) was estimated over the sampling period and does not represent the true elimination t_{1/2}.*

Figure 10. Mean Oteseconazole Plasma Concentration-Time Plots (20 – 320 mg)



Source: Figure 11-1 of Applicant's ISR VMT-VT-1161-CL-001

Abbreviations: h, hour.

Based on power model analysis, the AUC of oteseconazole increased in a dose-proportional manner while C_{max} increased less than dose proportionally for the dose range of 20 mg to 320 mg ([Table 123](#)).

Table 123. Analysis of Dose Proportionality for Dose Range of 20 mg to 320 mg

Dependent Variable ^a	Null Hypothesis[H ₀]	Slope Parameter (β) Estimate ± SE	95% Confidence Interval		Goodness of Fit (r ²)
			Lower	Upper	
log(C _{max})	Slope = 1	0.7049 ± 0.06072	0.5806	0.8293	0.8280
log(AUC _{inf})	Slope = 1	0.9556 ± 0.07061	0.8107	1.100	0.8715

Source: Table 6-4 of Applicant's ISR VMT-VT-1161-CL-001
Abbreviations: SE, standard error.

Multiple Ascending Dose

Study VMT-VT-1161-CL-002 was a multiple ascending dose study to evaluate the PK, safety and tolerability of oteseconazole in 32 healthy adult subjects. Subjects were enrolled into 4 dosage groups of 40, 80, 160 and 320 mg in which they were randomized 3:1 to receive oteseconazole or placebo, respectively. Following an overnight fast of at least 10 hours, doses were administered 30 minutes after a standardized high-fat meal (900 kcal with 50% of caloric content from fat). Blood samples were collected pre-dose and at pre-specified times post-dosing for the 7 consecutive days of daily dosing. Subjects returned on Days 14, 21, 35, 28 and 49 for additional safety, PK and laboratory assessments. PK samples were assayed using a validated LC-MS/MS method. Pharmacokinetic assessments included: C_{max} , minimum plasma concentration (C_{min}), T_{max} , area under the curve to the last quantifiable time point ($AUC_{0-\tau}$), V_z/F , CL/F , accumulation ratio (R_{acc}), and $t_{1/2}$. C_{max} , C_{min} , T_{max} , area under the concentration-time curve during the dosing interval (AUC_{τ}), and $t_{1/2}$ were estimated by noncompartmental analysis. Additionally, a two-compartment model with first order absorption and a lag-time for absorption was used in compartmental analysis to improve estimates for CL/F and $t_{1/2}$.

Oteseconazole was well-tolerated and all but one subject (enrolled in the 80 mg cohort) failed to complete the study. This was due to the only adverse event (AE) (constipation) reported in this study and deemed unrelated to study drug. Consistent with its long half-life, significant accumulation was observed following repeat administration of oteseconazole, with the greatest accumulation observed at the highest dose ([Table 124](#)). Both C_{max} and AUC_{τ} increased in an approximately dose proportional manner over the 40 to 320-mg dose range. Generally, V_z/F increased with increasing dose; CL/F decreased between the 40 and 80-mg dose levels but remained similar between the 80 to 320-mg dose levels. Mean concentration-time profiles at each dose level are provided in [Figure 11](#).

Table 124. Mean (± SD) of Day 7 NCA PK Parameters

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{τ} (h·ng/mL)	C_{min} (ng/mL)	R_{acc}	$t_{1/2}$ (h)
40	531 (106)	4.00 (0.00)	10202 (2287)	315 (71.4)	4.76 (0.31)	2103 (1060)
80	1130 (379)	6.80 (1.10)	23143 (8862)	742 (315)	4.46 (0.78)	2445 (1426)
160	1920 (445)	5.00 (1.10)	38661 (9787)	1250 (319)	4.62 (1.17)	3227 (1570)
320	3300 (859)	5.01 (1.68)	67164 (18034)	2240 (704)	6.16 (2.46)	5207 (3934)

Source: Table 11-3 of Applicant's ISR VMT-VT-1161-CL-002

Abbreviations: AUC_{τ} , area under curve during dosing interval; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; NCA, noncompartmental analysis; PK, pharmacokinetic; R_{acc} , accumulation ratio; $t_{1/2}$, half-life; T_{max} , time to maximum plasma concentration.

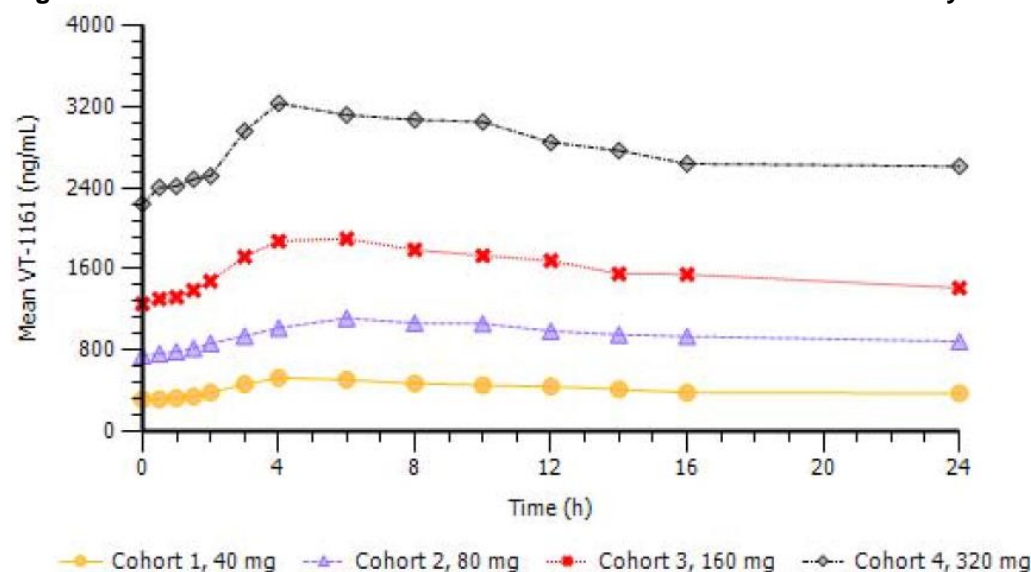
Table 125. Mean ($\pm$ SD) Compartmental PK Parameters

Dose (mg)	T _{lag} (h)	t _{1/2} β (h)	CL/F (L/h)	V _z /F (L)
40	1.92 (0.59)	1593 (882)	0.37 (0.12)	122 (19)
80	1.90 (0.40)	2567 (2049)	0.25 (0.14)	116 (18)
160	1.60 (0.70)	2704 (1149)	0.24 (0.11)	160 (29)
320	1.60 (0.35)	4324 (2949)	0.20 (0.14)	215 (34)

Source: Table 6-6 of Applicant's ISR VMT-VT-1161-CL-002

Abbreviations: CL/F, apparent clearance; PK, pharmacokinetic; t_{1/2}, half-life; T_{lag}, lag time; TV_z/F, apparent volume of distribution during terminal phase.

Figure 11. Mean Oteseconazole Plasma Concentration-Time Profiles at Day 7



Source: Figure 11-2 of Applicant's ISR VMT-VT-1161-CL-002

Abbreviations: h, hour.

VMT-VT-1161-CL-008: Multiple Dose and PK in Healthy Western Versus Japanese Subjects

Study CL-008 was a Phase 1, open-label study to determine the safety, tolerability and PK of multiple doses of 300 mg and 600 mg oteseconazole in healthy Western and Japanese subjects. A total of 51 subjects, 25 Japanese and 26 Western healthy volunteers were randomized to receive either 300 mg or 600 mg. Doses were administered at the clinical study site 30 min after the start of breakfast once daily for 14 days. Blood samples were collected pre-dose and at Days 2-12, Day 14-17 and at the Day 28 follow-up visit. Subjects returned on Days 14, 21, 35, 28 and 49 for additional safety, PK and laboratory assessments. PK samples were assayed using a validated LC-MS/MS method. Pharmacokinetic assessments included: C_{max}, C_{min}, T_{max}, area under the curve from 0 to 72 hours (AUC_{0-72h}) (for the Day 14 dose), V_z/F, CL/F and t_{1/2}, which were summarized using noncompartmental analysis.

As with previous studies, oteseconazole was well tolerated. In the 300-mg dose group, 11 out of 13 Japanese and 12 out of 14 Western subjects completed the study. One Japanese subject discontinued the study due to AEs; other discontinuations were due to physician decision, protocol violation and withdrawal by subject. Similarly, in the 600-mg dose group, 10 out of 12 Japanese subjects and all 12 Western subjects completed the study. Discontinuations at the

higher dose level were due to protocol violation and withdrawal by subject. [Table 126](#) summarizes PK parameters by dose level for Japanese and Western subjects.

Reviewer's Comment: At the 300-mg dose level, C_{max} and AUC_{0-72h} were ~32% and 20% higher, respectively, in Japanese subjects. At the 600-mg dose level, these differences in C_{max} and AUC_{0-72h} were ~17% and 5%, respectively. The reason underlying the small difference in exposure at the 300-mg dose level may be due to differences in body weight, which was shown to be a covariate for oteseconazole exposure in the population PK model. In the 300 mg cohorts, mean body weight for Japanese subjects was 60.25 kg, compared to 76.46 kg in Western subjects (i.e., ~27% lower body weight in Japanese subjects). In the 600 mg cohorts, this difference was less pronounced (67.29 kg versus 71.27 kg). Given the lack of difference in the safety and tolerability of oteseconazole between populations, these differences in exposure are not expected to be clinically significant.

Table 126. Mean Oteseconazole Plasma PK Parameters in Japanese Versus Western Subjects

Parameter (unit) Statistic	VT-1161 300 mg		VT-1161 600 mg	
	Japanese Subjects (N=11)	Western Subjects (N=12)	Japanese Subjects (N=11)	Western Subjects (N=12)
C_{max} (ng/mL)				
N	11	12	11	12
Mean	9370.9	6576.7	15576.4	14104.2
Standard Deviation	2103.23	1485.32	4180.54	4198.62
CV%	22.4	22.6	26.8	29.8
Median	8680.0	6575.0	15000.0	12850.0
Minimum, Maximum	6350, 12300	3470, 9210	8940, 24400	9450, 24100
T_{max} (hr)				
N	11	12	11	12
Mean	6.09	6.28	5.41	5.85
Standard Deviation	6.188	2.668	3.262	2.748
CV%	101.6	42.5	60.3	47.0
Median	4.00	6.00	4.00	6.00
Minimum, Maximum	2.0, 24.0	3.0, 10.3	1.5, 12.0	2.0, 10.2
AUC₀₋₇₂ (hr*ng/mL)				
N	11	12	11	12
Mean	595426.69	421433.74	982017.99	894336.42
Standard Deviation	152764.264	101111.142	307143.239	250434.798
CV%	25.7	24.0	31.3	28.0
Median	538229.50	422455.21	900275.00	852537.50
Minimum, Maximum	400335.0, 818809.2	226837.5, 627957.5	584813.0, 1715836	566007.5, 1468617
$t_{1/2}$ (hr)				
N	10	12	11	8
Mean	1834.96	2379.34	58482.40	3117.97
Standard Deviation	788.487	1279.237	181574.994	1839.872
CV%	43.0	53.8	310.5	59.0
Median	1514.47	2378.14	4390.84	2753.12
Minimum, Maximum	1012.7, 2903.7	754.5, 4269.3	365.8, 605858.7	1112.7, 6844.7
λ_z (1/hr)				
N	10	12	11	8
Mean	0.00045	0.00041	0.00043	0.00030
Standard Deviation	0.00018	0.00027	0.00054	0.00017
CV%	40.9	65.9	123.8	57.0
Median	0.00046	0.00029	0.00016	0.00025
Minimum, Maximum	0.00024, 0.00068	0.00016, 0.00092	0.00000, 0.00189	0.00010, 0.00062
CL/F (L/hr)				
N	10	12	11	8
Mean	1.642	2.332	2.000	2.086
Standard Deviation	0.420	0.665	0.556	0.601
CV%	25.6	28.5	27.8	28.8
Median	1.663	2.190	1.940	1.909
Minimum, Maximum	1.142, 2.282	1.508, 4.123	1.116, 3.218	1.299, 3.109

Source: Appendix 16.2.6.2, Section 14 Table 14.2.3

Abbreviations: λ_z , elimination rate constant; AUC₀₋₇₂, area under the curve from hour 0-72; CL/F, apparent clearance; C_{max} , maximum plasma concentration; CV%, coefficient of variation; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max} , time to maximum plasma concentration.

Food Effect

Study VMT-VT-1161-CL-013 was a Phase 1, open-label study intended to assess the effect of high-fat, high-calorie and low-fat, low-calorie meals on the bioavailability of oteseconazole. This study was also intended to bridge the (b) (4) tablet formulation used in Phase 1 extrinsic factor studies and Phase 2b studies to the Phase 3 capsule formulation. To meet these goals, 44 healthy adult females were allocated to 1 of 4 cohorts as follows:

- Fasted cohort (N=12): received a single 150 mg capsule on following an overnight fast of at least 10 h
- High-fat, high-calorie fed cohort (N=12): received a 150 mg capsule 30 minutes after the start of a high-fat, high-calorie meal (900-1000 kcal with 500-600 kcal from fat)
- Low-fat, low-calorie fed cohort (N=12): received a 150 mg capsule 30 minutes after the start of a low-fat, low-calorie meal (650 kcal with 117 kcal from fat)
- Comparative bioavailability cohort (N=8): received a (b) (4) 150-mg tablet 30 minutes after the start of a high-fat, high-calorie meal.

Reviewer's Comment: *Although the total caloric content of the low-fat, low-calorie meal exceeds the 400-500 kcal recommended by the FDA guidance for industry titled, "Assessing the Effects of Food on Drugs in INDs and NDAs" (February 2019), the total number of kcal from fat falls within the recommended 100-125 kcal range for such as meal.*

PK samples were collected pre-dose and through 72 h post-dose and analyzed using a validated LC-MS/MS method for assessment of the following PK parameters: C_{max} , T_{max} , $AUC_{0-\infty}$, AUC_{0-72h} , V_z/F , CL/F , and $t_{1/2}$. To assess the impact of food on oteseconazole exposure, an analysis of variance (ANOVA) was conducted using cohort designation as fixed effect. Least-square means of C_{max} and AUC_{0-72h} were estimated to obtain the geometric mean ratios (GMRs) for the fed versus fasted cohorts.

With the exception of 1 subject (in the low-fat, low-calorie fed cohort) who experienced vomiting 4 h post-dosing, all other subjects completed the study and were included in the PK analysis. High-fat, high-calorie food was found to increase the C_{max} and AUC_{0-72h} by 45% and 36%, respectively as summarized in [Table 127](#). However, following administration of a low-fat, low-calorie meal, C_{max} and AUC_{0-72h} increased by only 17% and 2%, respectively ([Table 128](#)). Under fed conditions, C_{max} and AUC_{0-72h} associated with the 150 mg (b) (4) tablet was comparable to that of the Phase 3 150 mg capsule formulation as shown in [Table 129](#).

Table 127. Comparison of Oteseconazole Plasma PK Parameters Under Fasted vs. Fed (High-Fat, High-Calorie) Conditions

Parameter	Cohort 2 (Test)		Cohort 1 (Reference)		GMR (%)	90% Confidence Interval	Inter-subject CV%
	Geometric LSM	n	Geometric LSM	n			
AUC ₀₋₇₂ (ng*hr/mL)	23200	12	17110	12	135.64	114.98 - 160.00	24.23
C _{max} (ng/mL)	781.2	12	538.0	12	145.20	119.05 - 177.09	29.31

Cohort 1: A single 150 mg VT-1161 capsule, fasted (Reference)
Cohort 2: A single 150 mg VT-1161 capsule, high-fat, high-calorie meal (Test)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric mean ratio (GMR) = 100 x (test/reference)
Inter-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: [Table 14.2.1.10](#)
Program: /CA24091/sas_prg/pksas/adam_intext_statsmixed.sas 31AUG2018 11:56

Abbreviations: ANOVA, analysis of variance; AUC₀₋₇₂, area under the curve from hour 0-72; C_{max}, maximum plasma concentration; CV%, coefficient of variation; MSE, mean squared error; PK, pharmacokinetic.

Table 128. Comparison of Oteseconazole Plasma PK Parameters Under Fasted vs. Fed (Low-Fat, Low-Calorie) Conditions

Parameter	Cohort 3 (Test)		Cohort 1 (Reference)		GMR (%)	90% Confidence Interval	Inter-subject CV%
	Geometric LSM	n	Geometric LSM	n			
AUC ₀₋₇₂ (ng*hr/mL)	17430	11	17110	12	101.88	86.04 - 120.63	24.23
C _{max} (ng/mL)	629.3	11	538.0	12	116.98	95.48 - 143.31	29.31

Cohort 1: A single 150 mg VT-1161 capsule, fasted (Reference)
Cohort 3: A single 150 mg VT-1161 capsule, low-fat, low-calorie meal (Test)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric mean ratio (GMR) = 100 x (test/reference)
Inter-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Subject 12, who received Cohort 3 (low-fat, low-calorie fed), vomited 4 hours after dosing; therefore, data from this subject was excluded from statistical analysis.
Source: [Table 14.2.1.11](#)
Program: /CA24091/sas_prg/pksas/adam_intext_statsmixed.sas 31AUG2018 11:56

Abbreviations: ANOVA, analysis of variance; AUC₀₋₇₂, area under the curve from hour 0-72; C_{max}, maximum plasma concentration; CV%, coefficient of variation; MSE, mean squared error; PK, pharmacokinetic.

Table 129. Oteseconazole Plasma PK Parameters for 150 mg (b) (4) Tablet Compared to the 150 mg (b) (4) Capsule Under Fed Conditions

Pharmacokinetic Parameters	Cohort 2	Cohort 4
AUC ₀₋₇₂ (ng*hr/mL)	23200 (30.4) [n=12]	20600 (17.1) [n=8]
C _{max} (ng/mL)	781.2 (34.9) [n=12]	793.7 (18.6) [n=8]
T _{max} (hr)	6.000 (3.99, 24.01) [n=12]	6.001 (2.00, 8.00) [n=8]

Cohort 2: A single 150 mg VT-1161 capsule, high-fat, high-calorie meal (Reference)
Cohort 4: A single 150 mg VT-1161 tablet, high-fat, high-calorie meal (Test)
AUC₀₋₇₂ and C_{max} values are presented as geometric mean and geometric CV%.
T_{max} values are presented as median (minimum, maximum).
Source: [Tables 14.2.1.6 and 14.2.1.8](#)
Program: /CA24091/sas_prg/pksas/adam_intext_pkparam.sas 31AUG2018 11:54

Abbreviations: AUC₀₋₇₂, area under the curve from hour 0-72; C_{max}, maximum plasma concentration; CV%, coefficient of variation; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration.

Mass Balance

Study VMT-VT-1161-CL-016

Study CL-016 evaluated the mass balance, safety and tolerability of oteseconazole in 10 healthy adult female subjects of nonchildbearing potential, following administration of a single 600 mg oral dose of [¹⁴C]oteseconazole containing 5 μCi of radiocarbon with a high-fat, high-calorie meal. Subjects remained at the clinical study site for 17 days post-dosing for collection of blood and excreta samples, returning for 5 in-patient visits at prespecified timepoints through Study Day 279 (approximately 10 months post-dosing).

In anticipation of variability daily fecal excretion volume and contents, in-patient follow-up visits spanned 3 days to provide 48 consecutive hours of continuous fecal collection. 24 h radiolabel fecal excretion was then determined as half of the total 48 h recovery during the confinement period. Recovery of radioactivity in urine and feces was interpolated between scheduled study visits. For urine, the following equation was used:

$$\frac{\%d + \%f}{2} \times ((tf - 1) - td) + \%f, \text{ where:}$$

%d = radioactivity in % collected from the last collection interval prior to follow-up

%f = radioactivity in % collected from the follow-up visit sample

tf = study day of the follow-up visit

td = study day of the last collection interval prior to follow-up

For feces, a modified equation was implemented, correcting for variable feces voiding as follows:

$$\frac{Cd + Cf}{24h} \times \left[\frac{\sum Wh}{408h} \times (hd - hf) \right], \text{ where:}$$

Cd = concentration in feces sample collected from the last collection interval prior to follow-up (dpm/g)

Cf = concentration in feces sample collected from the follow-up visit (dpm/g)

ΣWh = estimated weight of feces produced between collections (g)

24 h = hours in a day; 408 h = hours during initial confinement

hf = hour at end of collection period prior to follow-up (h)

hd = hour at start of collection period of the follow-up visit (h)

Analytical Methods

Quantitation of oteseconazole in plasma was performed using a validated LC-MS/MS method with an LLOQ of 20.0 ng/mL and upper limit of quantification of 40,000 ng/mL. Radioanalysis of urine and fecal homogenate samples was conducted using liquid scintillation counting; urine samples were added directly to a liquid scintillant and feces homogenate was combusted in a sample oxidizer for analysis. Samples were counted for at least 10 min or until 2%2σ terminator was reached. For liquid scintillation counting, LLOQ was defined as twice the background count rate, and samples below LLOQ were analyzed by accelerator mass spectrometry. Plasma and

blood samples were also analyzed by accelerator mass spectrometry and the LLOQ was defined as 15% above the percentage Modern Carbon (i.e., pMC which equals 0.01356 dpm/mg) value in pre-dose samples of the same source and matrix. Plasma samples collected following the initial confinement underwent metabolite profiling via high-performance liquid chromatography followed by accelerator mass spectrometry analysis.

Results

The median age of the 10 subjects enrolled in this study was 55.5 (range: 46 – 61) years. Of these, 8 subjects completed the study. PK data from subjects who withdrew from the study were included in average statistics until the time of their discontinuation from the study. Within the first 408 h, the mean cumulative recovery of radioactivity was only 8.92%, 6.32% of which was recovered in feces and 2.29% in urine as summarized in in [Table 130](#). At the termination of the study (Day 278), the mean total recovered radioactivity was <90%, i.e., $81.6 \pm 9.68\%$ (range: 64.1 - 95.3%) due to oteseconazole's exceptionally long half-life. Feces accounted for $56.0 \pm 12.3\%$ (range: 30.9 - 70.1%) of the recovered radioactivity while urine accounted for $25.6 \pm 10.3\%$ (range: 12.1 - 33.2%).

Table 130. Mean Cumulative Recovery (% Dose) of Total Radioactivity in Urine and Feces Following a Single Oral Dose of [¹⁴C] Oteseconazole to Healthy Female Subjects

Time (h)	Total		Feces		Urine	
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD
0-24	0.498	0.303	0	0	0.238	0.0561
0-48	2.02	1.63	0.261	0.324	0.427	0.0889
0-72	2.61	1.56	1.60	1.66	0.571	0.136
0-96	3.05	1.42	2.05	1.61	0.690	0.176
0-120	3.57	1.50	2.37	1.49	0.820	0.216
0-144	3.99	1.43	2.76	1.60	0.955	0.273
0-168	4.49	1.36	3.04	1.54	1.09	0.306
0-192	4.84	1.37	3.41	1.49	1.22	0.340
0-216	5.32	1.35	3.63	1.46	1.35	0.393
0-240	5.79	1.50	3.99	1.45	1.47	0.441
0-264	6.14	1.45	4.34	1.61	1.57	0.489
0-288	6.62	1.27	4.58	1.56	1.67	0.526
0-312	6.98	1.29	4.98	1.34	1.75	0.543
0-336	7.42	1.53	5.25	1.30	1.86	0.578
0-360	8.08	1.33	5.78	1.52	2.00	0.622
0-384	8.45	1.26	6.08	1.47	2.14	0.657
0-408	8.92	1.18	6.32	1.42	2.29	0.705
0-648*	10.4	1.29	6.62	1.31	3.77	1.31
0-672	10.5	1.32	6.62	1.31	3.90	1.36
0-1272*	23.3	2.98	6.62	1.31	6.88	2.64
0-1296	23.8	3.04	16.5	2.26	6.99	2.67
0-1320	24.2	3.15	16.8	2.23	ND ¹	ND ¹
0-2616*	42.3	4.97	17.2	2.32	12.4	4.50
0-2640	42.6	5.03	29.9	5.57	13.2	5.08
0-2664	42.8	4.99	30.1	5.61	ND ¹	ND ¹
0-3936*	59.6	6.97	30.3	5.61	18.3	7.02
0-3960	60.0	7.04	41.8	8.75	18.4	7.06
0-3984	60.2	7.04	42.0	8.73	ND ¹	ND ¹
0-5304*	74.6	9.66	42.2	8.74	22.5	8.90
0-5328	74.8	9.70	52.0	11.5	22.6	8.91
0-5352	74.9	9.75	52.1	11.6	ND ¹	ND ¹
0-6648*	81.4	9.69	52.2	11.6	25.5	10.3
0-6672	81.5	9.73	55.9	12.3	25.6	10.3
0-6696	81.6	9.68	56.0	12.3	ND ¹	ND ¹

ND=no data; SD=standard deviation.

¹Urine collections were 24-hr collections.

Source: Table 6, Table 7, Table 9, Determination of ¹⁴C-content in plasma, whole blood, urine, and feces samples derived from humans administered an oral dose of [¹⁴C]-VT-1161 (5 µCi/600 mg), dated 08Jan2021, Appendix 16.1.13.1.3.

*Intervals with interpolated values designated with an asterisk
Abbreviations: h, hour.

Reviewer's Comment: Of note, the Applicant's rat ADME study evaluated mass balance in both bile duct cannulated and intact male rats orally administered [¹⁴C]-oteseconazole containing

200 $\mu\text{Ci/kg}$. In this study, mean % recovery of total radioactivity was 62.5% after 120 h in cannulated rats and 85.7% through 504 h post-dosing in intact rats. Interestingly, the % recovery of radioactivity in feces through 120 h post-dosing was similar in cannulated and intact rats (i.e., 42% versus 47%, respectively). Approximately 26-29% of total radioactivity was recovered in feces within the first 24 h in the two rat cohorts, which was attributed to unabsorbed drug or intestinal secretion. Only 20% of the total radioactivity was recovered in bile, with 0.7% of the administered dose recovered in feces.

In humans, however, only 6.32% of total radioactivity was recovered in feces within the first 408 h post-dosing, which the Applicant assumes to be unabsorbed drug. *In vitro*, oteseconazole was not a substrate of the P-gp and BCRP intestinal efflux transporters. However, the Applicant did not determine if oteseconazole is a substrate of MRP2, another intestinal transporter. Therefore, the contribution of intestinal secretion to the fecal recovery of radioactivity cannot be ruled out.

In addition to being expressed on the intestinal membrane, MRP2 is also expressed on the bile canalicular membrane along with MATE and BSEP. Because the Applicant did not determine if oteseconazole is a substrate of any of these transporters, their involvement in the disposition of oteseconazole cannot be ruled out. The majority of fecal recovery, which occurs after the initial 408 h confinement period, suggests the involvement of mechanisms other than excretion of unabsorbed oteseconazole and/or intestinal secretion. Based on the observed biliary recovery in the rat ADME study, biliary secretion of oteseconazole is also likely in humans. Therefore, the prolonged recovery of oteseconazole in feces may be primarily due to biliary secretion mediated by MRP2, MATE or BSEP efflux transporters.

All subjects who completed the study had quantifiable levels of plasma and whole blood radioactivity through the last sampling time of 6634 h post-dosing. The blood-to-plasma ratio of total radioactivity approximates 1, indicating that oteseconazole is equally distributed between blood cells and plasma (Table 131). Plasma total radioactivity and plasma oteseconazole exposures were comparable, as indicated by the respective AUC values summarized in Table 131. This observation, in addition to the finding that unchanged oteseconazole accounted for 97.1% of circulating plasma radioactivity in 0-408 h pooled plasma samples obtained for metabolite profiling, indicates that oteseconazole does not undergo significant metabolism. Consequently, urine and fecal samples were not analyzed for possible metabolites. The estimated terminal half-life of oteseconazole was ~2114 h (~88 days) and similar to the terminal half-life of radioactivity in plasma and whole blood (Table 131).

Table 131. PK Parameters of Plasma Oteseconazole and Plasma and Whole Blood Radioactivity

Parameter Mean (SD, %CV)	n	Plasma VT-1161	Plasma Radioactivity	Whole Blood Radioactivity
C_{max}^1	10	3507.000 (950.3689; 27.1)	3609.000 (779.1227, 21.6)	3205.000 (656.0699, 20.5)
T_{max} (h)	10	6.200 (1.9889, 32.1)	6.000 (1.8856, 31.4)	6.000 (1.8856, 31.4)
AUC_{last}^1	10	3494864.260 (1446509.5983, 41.4)	3351587.938 (1379668.4525, 41.2)	3192067.869 (1243954.8173, 39.0)
AUC_{0-inf}^1	9	4301156.522 (1263134.1087, 29.4)	4196317.888 (1250171.8491, 29.8)	3973507.016 (1066911.5845, 26.9)
λ_z (1/h)	9	0.0003 (0.0001, 19.1)	0.0003 (0.0001, 18.5)	0.0003 (0.0001, 19.9)
$t_{1/2}$ (h)	9	2114.012 (445.4530, 21.1)	2233.690 (460.3593, 20.6)	2224.827 (467.8559, 21.0)
CL/F (L/h)	9	0.150 (0.0420, 28.0)	-	-
V_z/F (L)	9	451.907 (155.5158, 34.4)	-	-

CV=coefficient of variance; Geom.=geometric; n=number of subjects with non-missing values; SD=standard deviation.

¹Units for C_{max} are ng/mL for plasma VT-1161 and ngEq/mL for plasma and whole blood radioactivity. Units for AUC_{last} and AUC_{0-inf} are h*ng/mL for plasma VT-1161 and h*ngEq/mL for plasma and whole blood radioactivity

%CV = $100 \times (SD/Mean)$, where SD and Mean are the standard deviation and arithmetic mean of untransformed data, respectively.

Geometric %CV = $100 \times \text{Sqrt}(e^{SD^{*2}} - 1)$, where SD is the standard deviation of natural log-transformed data.

Source: Table 4. PK Report, 22Sep2020. Appendix 16.1.13.3.

Abbreviations: λ_z , elimination rate constant; AUC_{0-inf} , area under the curve from hour 0 to infinite; AUC_{last} , area under the curve to the last quantifiable time point; CL/F, apparent clearance; C_{max} , maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, half-life; T_{max} , time to maximum plasma concentration; V_z/F , apparent volume of distribution during terminal phase.

Reviewer's Comment: *In the proposed labeling, the Applicant states that oteseconazole has an oral bioavailability of 94% based on mass balance study results. In response to an IR (dated July 21st 2021) which sought clarification on the Applicant's approach to determining oral bioavailability from mass balance study results, the Applicant offered the following explanation:*

- *Based on the expectation that elimination of oteseconazole continues after study termination on Day 278 (at which point cumulative 81.6% of radioactivity had been recovered), the Applicant anticipates that recovery would eventually reach 100%.*
- *The 6.32% of radioactivity excreted via feces during the first 408 h collection interval is exclusively nonabsorbed oteseconazole.*
- *Using the assumption that recovery would eventually reach 100% and that 6.32% of oteseconazole was excreted unabsorbed, the oral bioavailability of oteseconazole was estimated to be 94%.*

However, the final sampling timepoints suggest that recovery of radioactivity has plateaued around 81.6%. Thus, it's unclear that continued collection of excreta would culminate in 100% recovery of the radiolabeled dose. Therefore, it would be more appropriate to assume 81.6% cumulative recovery in estimating bioavailability. If 6.32% of oteseconazole is excreted as unabsorbed drug, and 81.6% of total radioactivity is recovered, the estimated oral bioavailability of oteseconazole is 75.3%.

Effect of Oteseconazole on the QTc Interval

The effect of oteseconazole on the QTc interval was evaluated in Study VMT-VT-1161-CL-018, a double-blind, randomized, multiple-dose, placebo- and positive-controlled, crossover study in 59 healthy female volunteers. Subjects were randomized to oteseconazole, moxifloxacin (positive control)/placebo or placebo/moxifloxacin in a 2:1:1 ratio. In the oteseconazole arm, 600 mg of oteseconazole was administered daily on Days 1-13 followed by a 1200-mg dose on Day 14. For the moxifloxacin/placebo arm, a single dose of 400 mg moxifloxacin was

administered on Day 1 followed by daily administration of placebo through Day 14. Finally, the placebo/moxifloxacin arm was administered placebo on Days 1-14 and a single dose of 400 mg moxifloxacin on Day 15. Blood samples and continuous electrocardiogram measurements were obtained at pre-specified timepoints pre-dose through Day 17 post-dose for the oteseconazole and the combined moxifloxacin/placebo arms. No significant QTc interval prolongation was detected for oteseconazole. The upper bound of the two-sided 90% CI for the mean change in QTc was -10.5 msec (please see the [QT Study Review](#) authored by the Interdisciplinary Review Team for Cardiac Safety Studies uploaded to DARRTS on December 8th, 2021).

Summary of Clinical Drug-Drug Interaction Studies

Evaluation of Inhibition/Induction Effect of Oteseconazole on Sensitive CYP3A4 Substrate (Study VMT-VT-1161-CL-007)

Oteseconazole was identified as a CYP3A4 inhibitor and inducer in vitro. Thus, the Applicant conducted a clinical DDI study to evaluate the inhibition and induction effect of oteseconazole on a prototypical sensitive CYP3A4 substrate, midazolam. Subjects were enrolled in a fixed sequence design to receive a single 2 mg oral dose of midazolam on Days 1, 3, and 16. Subjects received 14 daily 600 mg oral doses of oteseconazole (four 150-mg tablets) on Day 3 through Day 16. Midazolam and oteseconazole were administered in the morning 30 minutes after a high-fat, high-calorie meal. A validated LC-MS/MS method was used for quantification of oteseconazole and midazolam concentrations in plasma. No serious TEAEs were observed in the study.

The study results suggest that coadministration of oteseconazole did not result in clinically significant inhibition of midazolam metabolism and caused weak induction of CYP3A4 with a 36% decrease in AUC of midazolam on day 16 compared to AUC on day 1. Note that the dosage regimen used for oteseconazole in this study is 600 mg once daily for 14 consecutive days, but the proposed maintenance dose of oteseconazole is 150 mg weekly. The C_{max} of oteseconazole on Day 16 is approximately 3-fold higher than the therapeutic exposure for the targeted indications seen in the Phase 3 studies. Therefore, it is unlikely there is a significant DDI between oteseconazole and CYP3A4 substrates at the proposed maintenance dose of oteseconazole, and thus no dosage adjustment is needed for drugs that are CYP3A4 substrates when co-administered with oteseconazole.

Table 132. Relative Bioavailability of Midazolam in the Presence of Oteseconazole

Midazolam PK Parameter	Day 3/Day 1 Ratio (90% CI)	Day 16/Day 1 Ratio (90% CI)
ANOVA Model ^a		
C _{max} (ng/mL)	1.30 (1.12- 1.52)	0.97 (0.83 – 1.14)
AUC ₀₋₂₄ (h*ng/mL)	0.86 (0.73 – 1.01)	0.64 (0.54 – 0.75)
AUC _{0-∞} (h*ng/mL)	0.85 (0.72 – 1.00)	0.63 (0.53 – 0.75)
Mixed Model for Repeated Measures ^b		
C _{max} (ng/mL)	1.30 (1.18 – 1.44)	0.94 (0.83 – 1.08)
AUC ₀₋₂₄ (h*ng/mL)	0.86 (0.83 – 0.90)	0.623 (0.58 – 0.67)
AUC _{0-∞} (h*ng/mL)	0.85 (0.82 – 0.89)	0.617 (0.57 – 0.67)

Abbreviations: ANOVA=analysis of variance; AUC₀₋₂₄=area under the plasma concentration versus time curve from time zero to 24 hours; AUC_{0-∞}=area under the plasma concentration versus time curve from time 0 extrapolated to infinity; CI=confidence interval; C_{max}=maximum measured plasma concentration; GLS=geometric least square; PK=pharmacokinetics

^a The first three rows show the GLS means, ratios, and CIs from an ANOVA model with log-transformed PK parameter as the outcome and sampling day as fixed effects.

^b The last three rows show the GLS means, ratios, and CIs from mixed model for repeated measures with log-transformed PK parameter as the outcome with sampling day as categorical time variable. Kenward-Roger correction for the denominator degree of freedom was used and unstructured covariance matrix was assumed. The mixed model for repeated measures was used as a sensitivity analysis for the ANOVA model.

Source: CL-007 CSR Table 11

Evaluation of Inhibition Effect of Oteseconazole on P-gp and BCRP Substrates (Study VMT-VT-1161-CL-015)

Oteseconazole was identified as a potential BCRP inhibitor in vitro, therefore, the Applicant conducted a clinical DDI study with rosuvastatin, a probe substrate for the BCRP transporter to evaluate inhibition effect of oteseconazole on BCRP membrane transporters. Given the common clinical assessments of interactions with digoxin as a substrate for P-gp, this study was also performed to rule out potential clinically relevant interactions with this transporter. This was a Phase 1, single-center, open-label, DDI study in healthy adult subjects to evaluate the effects of multiple oral doses of oteseconazole on the PK of a single oral dose of digoxin, a probe substrate for the P-gp transporter, and a single dose of rosuvastatin. Subjects received 0.5 mg digoxin or rosuvastatin 20 mg on Days 1, 3, and 16 and 150 mg oteseconazole once daily (QD) on Days 3 through 16. All doses were administered in the morning 30 minutes after ingesting a high-fat, high-calorie meal. In this study, three different validated analytical methods (LC-MS/MS) were used for quantification of the plasma concentrations of digoxin, rosuvastatin, and oteseconazole.

Digoxin Cohort

The study results showed that C_{max} and area under the curve from 0 to 24 hours (AUC_{0-24h}) of digoxin were similar (differences in mean ratios were approximately 6 - 13%) following the coadministration of a single dose of 0.5 mg digoxin and multiple doses of 150 mg oteseconazole (Day 16) compared with digoxin alone (Day 1). However, AUC_{0-∞} of digoxin was increased by around 52% after single dose of oteseconazole and was decreased by around 40% after multiple doses of oteseconazole. It is to be noted that out of 47 subjects who completed the study, AUC_{0-∞} of digoxin was reported from only 9 subjects on day 1, 3 subjects on day 3 and 14 subjects on day 16. Per the study report, *the λz values could not be assigned for subjects if the R2 value was*

< 0.75, or the terminal elimination phase was not evident, and therefore, values for λ_z and its associated parameters, (i.e., $t_{1/2}$, $AUC_{0-\infty}$, CL/F , and V_z/F) were considered not calculable and were not reported. These are presented as missing in the PK parameter tables. As around 81% of subjects on day 1 and around 94% of subjects on day 3 were excluded for $AUC_{0-\infty}$ assessment, $AUC_{0-\infty}$ of digoxin is not a reliable PK parameter for DDI assessment in this study. As digoxin is a long half-life drug ($t_{1/2}$: 1.5-2 days), it is unknown whether AUC_{0-24h} of digoxin is a reliable PK parameter to evaluate the DDI study. A literature search was conducted to find out whether P-gp inhibitor can have an inhibition effect on digoxin within 24 hours. The results showed that the inhibition effect on digoxin by a P-gp inhibitor can be observed within 24 hours (e.g., capmatinib (Grande et al. 2021) and fostamatinib (Martin et al. 2015)). Therefore, C_{max} and AUC_{0-24h} of digoxin were used for DDI assessment in this study. The study results suggest that the C_{max} and AUC_{0-24h} of digoxin were not affected in the presence of single or multiple doses of oteseconazole. Note that the current study was conducted under the worst-case scenario as oteseconazole was given 150 mg daily for 14 days. Therefore, it is unlikely there is a significant DDI between oteseconazole and P-gp substrates at the proposed maintenance dose of oteseconazole, and thus no dosage adjustment is needed for drugs that are P-gp substrates when co-administered with oteseconazole.

Table 133. Digoxin PK Parameters-Summary of Statistical Comparisons

PK Parameter	Oteseconazole + Digoxin (Test)		Digoxin Alone (Reference)		GMR (%)	90% CI	Intra-subject CV%
	Geo LSM	n	Geo LSM	n			
Oteseconazole – Single Dose							
AUC_{0-24} (ng*hr/mL)	14.51	23	14.22	24	102.02	96.07 – 108.35	12.22
$AUC_{0-\infty}$ (ng*hr/mL)	87.10	3	57.24	9	152.16	71.96 – 321.75	52.47
C_{max} (ng/mL)	1.726	23	1.666	24	103.62	93.81 – 114.45	20.38
Oteseconazole – Multiple Doses							
AUC_{0-24} (ng*hr/mL)	15.10	23	14.22	24	106.19	100.46 – 112.24	11.25
$AUC_{0-\infty}$ (ng*hr/mL)	33.88	14	55.86	9	60.64	36.80 – 99.94	65.70
C_{max} (ng/mL)	1.881	23	1.666	24	112.92	102.55 – 124.34	19.72

Abbreviations: ANOVA=analysis of variance; AUC_{0-24} =area under the plasma concentration versus time curve from time 0 to 24 hours; $AUC_{0-\infty}$ =area under the plasma concentration versus time curve from time 0 extrapolated to infinity; CI=confidence interval; C_{max} =maximum measured plasma concentration; CV=coefficient of variation; geo=geometric; GMR=geometric mean ratio; LSM=least squares mean; PK=pharmacokinetic

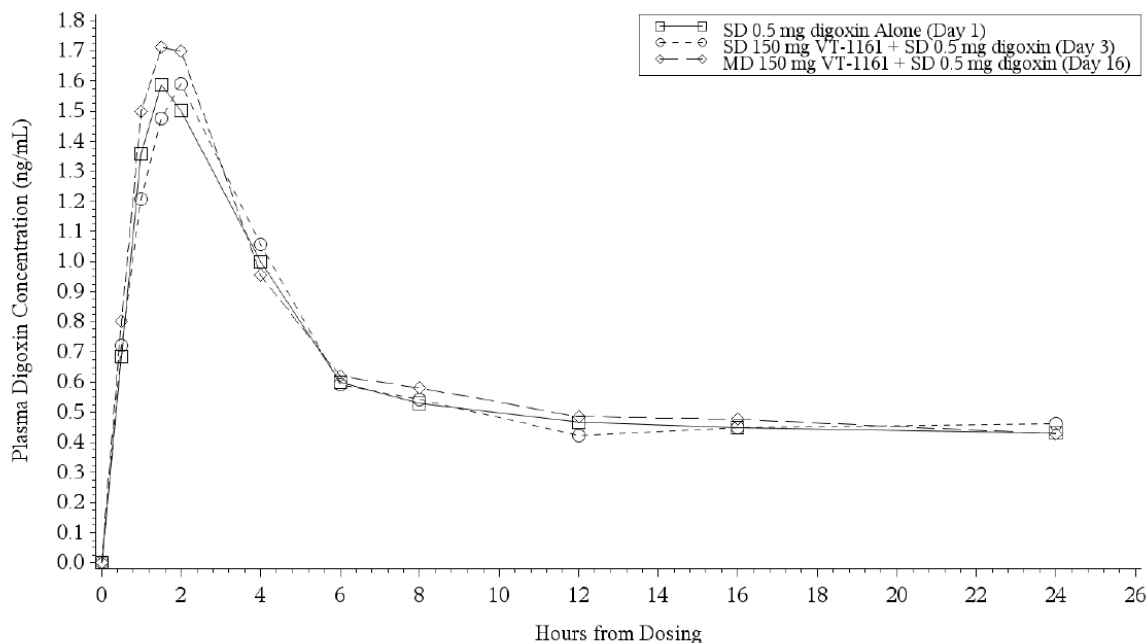
Note: Geometric LSMs were calculated by exponentiating the LSMs from the ANOVA.

Note: GMR=100*(test/reference).

Note: Intra-subject CV% was calculated as 100 x square root (exp[residual variance]-1), where MSE=Residual variance from ANOVA.

Source: CL-015 CSR Table 11-3 and Table 11-4

Figure 12. Mean Digoxin Plasma Concentrations Over Time Following the Administration of Digoxin Alone or Coadministration With Single or Multiple Doses of Oteseconazole (CL-015)



Day 3 data were baseline adjusted due to measurable pre-dose plasma concentrations.
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Source: Figure 14.2.2.1.2 of Applicant's ISR VMT-VT-1161-CL-015

Rosuvastatin Cohort

The statistical comparisons of plasma rosuvastatin PK parameters in the presence and absence of oteseconazole are summarized in [Table 134](#). Based on the geometric mean ratios, mean C_{max} , AUC_{0-24h} and $AUC_{0-\infty}$, were approximately 84% to 87% higher following coadministration of a single dose of 20 mg rosuvastatin and a single dose of 150 mg oteseconazole (Day 3) compared with the administration of rosuvastatin alone (Day 1). Based on the geometric mean ratios, mean C_{max} and AUC of rosuvastatin, were approximately 94% to 118% higher following the coadministration of a single dose of 20 mg rosuvastatin and multiples doses of 150 mg oteseconazole (Day 16) compared with the administration of rosuvastatin alone (Day 1). Therefore, it is concluded that oteseconazole is an inhibitor of BCRP.

Table 134. Rosuvastatin PK Parameters - Summary of Statistical Comparison

PK Parameter	Oteseconazole + Rosuvastatin (Test)		Rosuvastatin Alone (Reference)		GMR (%)	90% CI	Intra-subject CV%
	Geo LSM	n	Geo LSM	n			
Oteseconazole – Single Dose							
AUC ₀₋₂₄ (ng*hr/mL)	66.19	24	35.88	24	184.49	169.06 -201.32	18.17
AUC _{0-∞} (ng*hr/mL)	89.41	17	48.03	20	186.15	167.41 – 207.00	18.37
C _{max} (ng/mL)	7.424	24	3.971	24	186.94	167.62 – 208.50	22.81
Oteseconazole – Multiple Doses							
AUC ₀₋₂₄ (ng*hr/mL)	76.81	24	35.88	24	214.10	196.60 – 233.15	17.73
AUC _{0-∞} (ng*hr/mL)	93.03	24	48.05	20	193.63	175.80 – 213.27	18.53
C _{max} (ng/mL)	8.657	24	3.971	24	217.99	196.00 – 242.44	22.21

Abbreviations: ANOVA=analysis of variance; AUC₀₋₂₄=area under the plasma concentration versus time curve from time 0 to 24 hours; AUC_{0-∞}=area under the plasma concentration versus time curve from time 0 extrapolated to infinity; CI=confidence interval; C_{max}=maximum measured plasma concentration; CV=coefficient of variation; geo=geometric; GMR=geometric mean ratio; LSM=least squares mean; PK=pharmacokinetic

Note: Geometric LSMs were calculated by exponentiating the LSMs from the ANOVA.

Note: GMR=100*(test/reference).

Note: Intra-subject CV% was calculated as 100 x square root (exp[residual variance]-1), where MSE=Residual variance from ANOVA.

Source: CL-015 CSR Table 11-7 and Table 11-8

Reviewer’s Comment: Notably, the oteseconazole regimen used in this study (i.e., 150 mg daily for 14 days) yields C_{max} and AUC_{24h} values that are 30% and 16% higher than C_{max} and AUC_{24h}, respectively, at Week 13 for the recommended dosing regimen for RVVC. Thus, the results of this DDI study present the worst-case scenario for increases in rosuvastatin exposure when used concomitantly with oteseconazole.

Evaluation of the Effect of Oteseconazole on Oral Contraceptive (OC) (VMT-VT-1161-CL-014)

This was a Phase 1, single-center, open-label, DDI study in healthy adult females designed to evaluate the effects of multiple oral doses of oteseconazole tablets on the PK of single oral doses of an OC containing ethinyl estradiol (EE) and norethindrone (NE). A total of 24 subjects received a single oral dose of an OC containing a fixed-dose combination of 35 µg EE and 1 mg NE on Day 1 and Day 21 together with 150 mg oteseconazole on Days 8 through 21 in a fixed-sequence design. The objective of this study was to evaluate the effects of multiple oral doses of oteseconazole on the PK of a single oral dose of contraceptive drugs containing EE and NE.

As stipulated in the FDA draft guidance for industry entitled “*Clinical Drug Interaction Studies With Combined Oral Contraceptives*” (November 2020), an approximately 40 percent increase in EE concentration for combined oral contraceptives (COC) containing 35 µg EE resulting in exposures similar to COC containing 50 µg EE could be clinically meaningful. Based on the

GMRs, mean peak and extend of exposure to EE, as measured by mean C_{max} , AUC_{0-24h} , AUC_{0-t} , and $AUC_{0-\infty}$, were approximately 12% to 20% higher following multiple daily doses of oteseconazole. As the exposure increase is less than 40%, it is unlikely the proposed dosage regimen of oteseconazole would have a significant clinical impact on the EE's exposure.

Table 135. Summary of Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone Alone on Day 1 or Coadministration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone With Multiple Doses of 150 mg VT-1161 on Day 21 (PK Population)

Parameter	MD VT-1161 + SD EE/NE (Test)		EE/NE Alone (Reference)		GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSM	n	Geometric LSM	n			
AUC_{0-t} (pg*hr/mL)	939.3	24	835.4	24	112.43	106.19 - 119.04	11.58
AUC_{0-inf} (pg*hr/mL)	1136	24	1006	24	112.98	105.86 - 120.58	13.21
C_{max} (pg/mL)	65.53	24	54.48	24	120.29	106.05 - 136.44	25.89

MD VT-1161 + SD EE/NE: Multiple oral doses of 150 mg VT-1161 (1 x 150 mg) tablet administered QD on Days 8 - 21 with a single oral dose of 35 µg EE/1 mg NE (1 x 35 µg EE/1 mg NE tablet) coadministered on Day 21 (test)
 EE/NE Alone: A single oral dose of 35 µg EE/1 mg NE (1 x 35 µg EE/1 mg NE tablet) on Day 1 (reference)
 Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
 Geometric Mean Ratio (GMR) = 100*(test/reference)
 Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual Variance from ANOVA.
 Source: Table 14.2.1.1.6
 Program: /CA24090/sas_prg/pksas/adam_intext_statsmixed.sas 30AUG2019 10:10

Abbreviations: ANOVA, analysis of variance; AUC_{0-inf} , area under the curve from hour 0 to infinite; AUC_{0-t} , area under the curve to the last quantifiable time point; C_{max} , maximum plasma concentration; CV%, coefficient of variance; EE, ethinyl estradiol; MSE, mean squared error; PK, pharmacokinetic; NE, norethindrone.

The C_{max} , $AUC_{0-\tau}$, and $AUC_{0-\infty}$ of NE were similar following the coadministration of a single dose of 35 µg EE/1 mg NE with multiple doses of 150 mg oteseconazole on Day 21 and the administration of a single dose of 35 µg EE/1 mg NE alone on Day 1. Therefore, it is unlikely the proposed dosage regimen of oteseconazole would have a significant clinical impact on the exposure of NE. Overall, no clinically meaningful effect of the concomitant use of oral contraceptives with oteseconazole would be anticipated, and thus no dosage adjustment is needed.

Table 136. Summary of Statistical Comparisons of Plasma NE Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg EE/1 mg NE Alone on Day 1 or Coadministration of a Single Dose of 35 µg EE/1 mg NE With Multiple Doses of 150 mg Oteseconazole on Day 21

Parameter	MD VT-1161 + SD EE/NE (Test)		EE/NE Alone (Reference)		GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSM	n	Geometric LSM	n			
AUC _{0-t} (pg*hr/mL)	53120	24	56960	24	93.25	88.26 - 98.53	11.16
AUC _{0-inf} (pg*hr/mL)	56020	24	59760	24	93.74	88.61 - 99.17	11.41
C _{max} (pg/mL)	6247	24	6472	24	96.52	80.87 - 115.19	36.92

MD VT-1161 + SD EE/NE: Multiple oral doses of 150 mg VT-1161 (1 x 150 mg) tablet administered QD on Days 8 - 21 with a single oral dose of 35 µg EE/1 mg NE (1 x 35 µg EE/1 mg NE tablet) coadministered on Day 21 (test)
 EE/NE Alone: A single oral dose of 35 µg EE/1 mg NE (1 x 35 µg EE/1 mg NE tablet) on Day 1 (reference)
 Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
 Geometric Mean Ratio (GMR) = 100*(test/reference)
 Intra-subject CV% was calculated as 100 x square root(exp[MSE]-1), where MSE = Residual Variance from ANOVA.
 Source: Table 14.2.1.2.6
 Program: /CA24090/sas_prg/pksas/adam_intext_statsmixed.sas 30AUG2019 10:10

Abbreviations: ANOVA, analysis of variance; AUC_{0-inf}, area under the curve from hour 0 to infinite; AUC_{0-t}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; CV%, coefficient of variance; EE, ethinyl estradiol; MSE, mean squared error; NE, norethindrone

Phase 2 Studies

Study VMT-VT-1161-CL-004

Study CL-004 was a Phase 2a, randomized, double-blind, dose-ranging study to evaluate the efficacy and safety of oteseconazole in comparison to a single 150-mg dose of fluconazole in the treatment of subjects with moderate to severe acute vulvovaginal candidiasis. Subjects were initially randomized 3:3:2 to oteseconazole dosing regimens of 300 mg QD or 600 mg QD for 3 days, or a single dose of fluconazole (plus placebo to maintain blinding). Following an interim analysis of safety, efficacy and PK, a third oteseconazole dose level (600 mg twice daily [BID] for 3 days) was added to the study, and subjects were enrolled in a 3:1 ratio to the high dose oteseconazole arm and fluconazole, respectively. The primary efficacy objective was to evaluate the composite of clinical and mycological efficacy of the 3 oteseconazole dose levels compared to fluconazole at the test of cure (TOC) i.e., Day 28 visit. Secondary objectives included:

- Evaluation of the safety and tolerability of oteseconazole at the 3 dose levels
- Evaluation of clinical efficacy alone at the TOC
- Evaluation of mycological efficacy alone at Days 7, 14 and TOC
- Evaluation of PK of the 3 oteseconazole dose levels

Oteseconazole dose selection for this study was informed by the safety and PK of oteseconazole in SAD and MAD studies as well as findings from nonclinical studies in a murine model of vaginal candidiasis. Results from the murine studies indicated that plasma oteseconazole concentrations $\geq 1 \mu\text{g/mL}$ were associated with >90% median reduction in fungal burden. Based on the exposures observed in Phase 1 SAD and MAD studies, the 3 oteseconazole dosing regimens were predicted through modeling and simulation to yield C_{min} values in excess of the 1 µg/mL threshold.

Subjects were instructed to take study drug 30 minutes after consuming a meal, however the types and caloric contents of meals were not specified. Sparse PK sampling was conducted beginning at baseline through 168 days post-dosing and analyzed using a validated LC-MS/MS method. Additionally, samples were obtained from consenting subjects on Study Day 1 at pre-dose and 1, 2, 3, 4, 5, 6 and 8 h post-dosing. The oteseconazole plasma PK parameters of interest in this study were: C_{max} , C_{min} , T_{max} , area under the curve from 0 to 8 hours (AUC_{0-8h}) and $t_{1/2}$.

Of the 40 female subjects randomized to the oteseconazole treatment arms (where N = 12 to 15 subjects/treatment group), 35 subjects completed the study. Nineteen subjects treated with oteseconazole were reported to have TEAEs, none of which led to study discontinuation; five subjects who received oteseconazole were lost to follow-up. The primary efficacy endpoint of therapeutic cure was achieved in 64.3%, 75% and 78.6% of subjects in the 300 mg QD, 600 mg QD and 600 mg BID treatment arms, respectively, compared to 66.7% for fluconazole in the ITT population as summarized in [Table 137](#). Statistically, there was no significant difference in cure rates for any of the oteseconazole arms compared to fluconazole. PK parameters following single dose administration of 300 mg or 600 mg are summarized in [Table 138](#). Mean C_{min} values at 24 hours following the final dose were calculated using the estimated $t_{1/2}$ obtained on Days 7 to 168 and determined to be 0.71 $\mu\text{g/mL}$, 1 $\mu\text{g/mL}$ and 2.8 $\mu\text{g/mL}$ for the 300 mg QD, 600 mg QD and 600 mg BID treatment arms, respectively.

Per the Applicant, the comparatively higher cure rates for the 600 mg QD and 600 mg BID arms compared to the 300 mg QD arm may be attributed to the lower oteseconazole exposures (particularly C_{min}) in the low dose group.

Table 137. Percentage of Subjects With Therapeutic Cure at TOC Visit (Day 28)

	VT-1161 300 mg q.d.	VT-1161 600 mg q.d.	VT-1161 600 mg b.i.d.	Fluconazole
Per Protocol Population	N = 8	N = 7	N = 14	N = 8
Therapeutic Cure				
Yes	6 (75.0%)	6 (85.7%)	11 (78.6%)	5 (62.5%)
No	8 (25.0%)	1 (14.3%)	3 (21.4%)	3 (37.5%)
p-value ^a	0.9564	0.3711	0.3633	
mITT Population	N = 11	N = 8	N = 14	N = 9
Therapeutic Cure				
Yes	7 (63.6%)	6 (75.0%)	11 (78.6%)	6 (66.7%)
No	4 (36.4%)	2 (25.0%)	3 (21.4%)	3 (33.3%)
p-value ^a	0.6905	0.6567	0.5064	
ITT Population	N = 14	N = 12	N = 14	N = 15
Therapeutic Cure				
Yes	9 (64.3%)	9 (75.0%)	11 (78.6%)	10 (66.7%)
No	5 (35.7%)	3 (25.0%)	3 (21.4%)	5 (33.3%)
p-value ^a	0.5206	0.4963	0.2959	

Source: Table 11-12 of Applicant's ISR VMT-VT-1161-CL-004

Abbreviations: bid, twice daily; ITT, intent to treat; mITT, modified intent to treat; q.d., once daily; TOC, test of cure.

Table 138. Mean PK Parameters Following Single a Dose of 300 or 600 mg Oteseconazole

Dose (mg)	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-8h} (h·µg/mL)
300	0.41 (0.17)	4.21 (0.81)	1.87 (0.60)
600	0.97 (0.086)	5.75 (1.71)	4.23 (0.94)

Source: Table 4-1 of Applicant's Pharmacokinetics Report for Study VMT-VT-1161-CL-004

Abbreviations: AUC_{0-8h}, area under the curve from 0 to 8 hours; C_{max}, maximum plasma concentration; h, hour; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration

Reviewer's Comment: Numerically, the efficacy of the 300 mg QD regimen is comparable to that of the fluconazole arm, while the 600 mg treatment arms provide numerically higher efficacy rates. While the sample size is small, observations from the study support use of 600 mg QD as part of the loading dose/treatment of acute VVC.

Study VMT-VT-1161-CL-006

Study CL-006 was a Phase 2b, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of 4 oteseconazole dosing regimens for the prevention of culture-verified acute VVC through Week 48 (of the study) in subjects with RVVC. Secondary objectives were to:

- Evaluate the proportion of subjects with culture-verified acute VVC through Week 24
- Evaluate the safety and tolerability of the oteseconazole dosing regimens through Week 48
- Evaluate the PK of the 4 dosing regimens.

The study was conducted in two phases: subjects (N=254) were first enrolled in an induction phase in which they received 3 doses of 150 mg fluconazole administered every 72 h for the treatment of the acute episode of VVC, followed by a maintenance phase in which they were randomized to 1 of 5 treatment arms. Subjects who were determined to have resolution of their acute VVC infection at 14 days post-initiation of fluconazole treatment were then randomized to the 5 maintenance phase treatment arms as follows:

- 150 mg oteseconazole daily for 1 week + 150 mg oteseconazole weekly for 11 weeks + placebo for 12 weeks (N=42)
- 150 mg oteseconazole daily for 1 week + 150 mg oteseconazole weekly for 23 weeks (N=43)
- 300 mg oteseconazole daily for 1 week + 300 mg oteseconazole weekly for 11 weeks + placebo for 12 weeks (N=43)
- 300 mg oteseconazole daily for 1 week + 300 mg oteseconazole weekly for 23 weeks (N=41)
- Placebo daily for 1 week + placebo weekly for 23 weeks (N=46)

Selection of the oteseconazole dosing regimens was informed by safety and PK data from Phase 1 SAD and MAD studies, preclinical murine efficacy studies, and the Phase 2a dose-ranging study in subjects with acute VVC. Based on the results of these preceding studies, dosing regimens anticipated to yield C_{min} values ≥ 1 µg/mL were selected for evaluation. Subjects were instructed to take study drug 30 minutes after the main meal of the day at the same time of day throughout the study. Sparse PK sampling was conducted beginning at baseline through Week 48, and samples were analyzed using a validated LC-MS/MS method. Additionally, samples were obtained from consenting subjects on Study Day 7 at pre-dose and 1, 2, 3, 4, 5, 6 and 8 h post-dosing. For this study, the plasma PK parameters of interest were: C_{max}, C_{min}, T_{max} and AUC_{0-8h} (at Day 7).

A total of 39 subjects discontinued study participation prematurely, with the most commonly listed reason being loss to follow up (n=16). The number of subjects who completed the study was similar across treatment groups and there were no notable differences in the incidence of TEAEs across all treatment groups (including placebo). Two subjects (from the 150 mg and 300 mg 12-week treatment arms) experienced TEAEs leading to study discontinuation. For the primary endpoint, the percentage of subjects who experienced an acute VVC infection through Week 48 was lower in the oteseconazole treatment groups compared to placebo, and similar between oteseconazole treatment arms as summarized in [Table 139](#) (please see Sections [6.2](#) and [7.6](#) for detailed discussion of the safety and efficacy of oteseconazole in this study). As would be expected, exposures for the 150 mg 12 week and 24-week regimens were comparable, as were the exposures for the 300 mg 12 week and 24-week regimens ([Table 140](#)).

Table 139. Percentage of Subjects With 1 of More Culture-Verified Acute VVC Infections Through Week 48 (Intent-to-Treat Population)

Culture-Verified Acute VVC Infection		VT-1161				
		150 mg 12 Weeks (N=42)	150 mg 24 Weeks (N=43)	300 mg 12 Weeks (N=43)	300 mg 24 Weeks (N=41)	Placebo (N=46)
Yes	n (%)	2 (4.8%)	3 (7.0%)	0	2 (4.9%)	24 (52.2%)
	95% CI	(0.6%, 16.2%)	(1.5%, 19.1%)	(0.0%, 8.2%)	(0.6%, 16.5%)	(36.9%, 67.1%)
	Odds Ratio ^a	0.0308	0.0414	0.0000	0.0438	
	95% CI ^a	(0.0056, 0.1695)	(0.0088, 0.1944)	(N/A, N/A)	(0.0087, 0.2210)	
	P-value ^a	<0.0001	<0.0001	<0.0001	<0.0001	

Abbreviations: N/A, not applicable; VVC, vulvovaginal candidiasis.

Note: Culture-verified acute vulvovaginal candidiasis (VVC) infection was defined as a positive fungal culture for *Candida* species associated with clinical signs and symptoms score ≥ 3 . Percentage calculations assumed that subjects who discontinued the study prior to a culture-verified VVC episode (censored subjects) had no episodes. The 95% CIs for the proportion of subjects with 1 or more culture-verified acute VVC infections through Week 48 were calculated using an exact method (Clopper-Pearson).

^a Odds ratio, corresponding 95% CIs and p-values were from Cochran-Mantel-Haenszel tests comparing each VT-1161 treatment group to placebo stratified by site.

Source: Table 2-1 of Applicant's ISR VMT-VT-1161-CL-006

Table 140. Summary of Oteseconazole PK by Treatment Arm

PK Parameter	150 mg	150 mg	300 mg	300 mg
	12 Weeks	24 Weeks	12 Weeks	24 Weeks
C _{max} (µg/mL) (SD)	1.34 (1.02)	1.80 (1.06)	2.75 (1.13)	3.12 (1.28)
T _{max} (hr) (Min-Max)	4.00 (0.00-6.00)	4.93 (2.00-5.00)	4.92 (2.00-6.00)	5.00 (2.00-8.00)
AUC ₈ (µg*hr/mL) (SD)	9.12 (7.25)	12.3 (6.30)	20.5 (6.02)	21.6 (9.14)

Abbreviations: AUC₈, area under the plasma concentration-time curve from pre-dose to 8 hours post-dose at the Day 7 visit; C_{max}, maximum plasma concentration at the Day 7 visit; Max, maximum; Min, minimum; PK, pharmacokinetic; T_{max}, time to reach the maximum plasma concentration at the Day 7 visit.

Source: Table 11-28 of Applicant's ISR VMT-VT-1161-CL-006

Reviewer's Comments: *Although exposures associated with the 300 mg regimens were ~2-fold what was observed with the 150 mg regimens, numerically, efficacy rates were comparable across oteseconazole treatment arms. Therefore, results from this study support further evaluation of the 150 mg 12-week regimen for the prevention of recurrence in Phase 3 trials.*

Phase 3 Studies

Studies VMT-VT-1161-CL-011 and VMT-VT-1161-CL-012

Studies CL-011 and CL-012 were identically designed Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled studies. These studies were designed to evaluate the efficacy and safety of oral oteseconazole capsules in the treatment of recurrent vulvovaginal candidiasis in females aged 12 years and older. Both studies were conducted in 2 phases as follows:

- An open-label induction phase using 3 doses of 150 mg oral fluconazole administered every 72 h for the treatment of the acute VVC episode present at the time of screening
- A maintenance phase in which subjects were randomized 2:1 to receive either 150 mg oteseconazole or placebo daily for 7 days followed by weekly dosing for 11 weeks beginning 1 week after completion of daily dosing regimen.

Selection of the oteseconazole dosing regimens was informed by safety and PK data from Phase 1 SAD and MAD studies, preclinical murine efficacy studies, and the two Phase 2 dose-ranging studies conducted in subjects with acute and recurrent VVC. Given that the 150 mg 12-week regimen was as efficacious as the higher dose and longer duration regimens in the Phase 2b study, it was expected to be sufficient for the prevention of recurrence of VVC. The primary efficacy endpoint was defined as the proportion of subjects who experienced 1 or more episodes of culture-verified acute VVC (considered a recurrent episode) during the maintenance phase in the ITT population. The secondary endpoints included:

- Time to first recurrence of culture-verified acute VVC episode with signs and symptoms score ≥ 3 during the maintenance phase
- Proportion of subjects with at least 1 positive culture for *Candida* during the maintenance phase
- Proportion of subjects with at least 1 culture-verified acute VVC episode with signs and symptoms score ≥ 3 post-randomization through Week 24

To ensure compliance, subjects were instructed to ingest study medication within 30 minutes after their main meal of the day (as determined by the subject) at approximately the same time of day. Blood samples were obtained from a small cohort of Phase 3 subjects pre-dosing, at Day 14 and prior to weekly drug product administration on Weeks 12, 24, 36 and 48 post administration of the first dose of oteseconazole. Plasma samples were analyzed using a validated LC-MS/MS method.

Reviewer's Comment: *The type and caloric contents of foods administered with oteseconazole was not recorded. At the End-of-Phase 2 meeting discussions, the clinical pharmacology team agreed with the Applicant's plan to have oteseconazole administered with the day's largest meal (of the subject's choosing) as long as dosing instructions were clearly detailed in the study protocol.*

In Study CL-011, 217 subjects were randomized to receive oteseconazole and 109 subjects were randomized to the placebo arm. Similarly, 217 subjects were also randomized to the oteseconazole arm in Study CL-012 while 110 subjects were randomized to placebo. Oteseconazole was well tolerated in both studies; 182 subjects in study CL-011 and 191 subjects in Study CL-012 completed their respective studies and most early discontinuations were

attributed to subject withdrawal of consent (please see Sections 6.2 and 7.6 for detailed discussion of the safety and efficacy of oteseconazole in this study). Mean oteseconazole plasma concentrations observed in studies CL-011 and CL-012 were comparable and are summarized by study visit in [Table 141](#).

Table 141. Oteseconazole C_{min}(ng/mL) Presented as Mean (SD)

Visit	Study CL-011	Study CL-012
Day 14	1676.2 (876.3)	1785.5 (747.8)
Week 12	3402.4 (1970.5)	3605.8 (1518.1)
Week 24	2477.8 (1487.4)	2588.6 (1070.7)
Week 36	1753.9 (1102.4)	1779.0 (930.9)
Week 48	1148.5 (833.7)	1122.0 (656.1)

Source: Table 11-8 of Applicant's ISRs VMT-VT-1161-CL-011 and VMT-VT-1161-CL-012
Abbreviations: C_{min}, minimum plasma concentration.

Study VMT-VT-1161-CL-017

Study CL-017 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study intended to evaluate the efficacy and safety of oteseconazole for the treatment of acute VVC in females with RVVC aged 12 years and older. As with the preceding studies CL-011 and CL-012, study CL-017 was conducted in two phases as follows:

- 2:1 randomization (N=219) to induction with either 600 mg oteseconazole on Day 1 and 450 mg on Day 2 or 3 doses of 150 mg fluconazole administered 72 h apart to treat the acute infection
- Beginning on Day 14, maintenance dosing with 150 mg oteseconazole or placebo (for the fluconazole induction arm) weekly for 11 weeks

Although the oteseconazole induction dosing regimen was not explicitly studied in previous Phase 2 studies, this regimen was expected to yield clinically effective oteseconazole plasma concentrations (i.e., ≥ 1 $\mu\text{g/mL}$ based on previous Phase 2 studies) for the treatment of acute VVC. The primary endpoint was the proportion of subjects with 1 or more culture verified acute VVC episodes post-randomization through Week 50 in the ITT population. Secondary endpoints included:

- Proportion of subjects with at least 1 positive culture for *Candida* during the maintenance phase (post-Day 14 through Week 50)
- Proportion of subjects with at least 1 culture verified acute VVC episode with signs and symptoms score ≥ 3 during the maintenance phase

As with studies CL-011 and CL-012, subjects were instructed to take study medication within 30 minutes after their main meal of the day. Blood samples for oteseconazole PK assessment were obtained at pre-dose and at Day 14, Week 14 (end of dosing) and Week 50 (end of follow-up period) post initiation of treatment. Additional PK samples were obtained from a small subset of consenting subjects on Days 1 and 2 (at 1, 2, 4 and 8 h post-dosing) to facilitate noncompartmental analysis. Plasma samples were analyzed using a validated LC-MS/MS method.

Of the 219 subjects entered into the induction phase, 147 were randomized to the oteseconazole group and of these, 35 total subjects discontinued the study prematurely largely due to induction failure (n=22). The proportion of subjects with 1 or more culture verified acute VVC episodes post-randomization through Week 50 in the ITT population was lower in the oteseconazole arm

(5.1%) compared to the fluconazole + placebo arm (42.2%); this difference was found to be statistically significant (please see Sections 6.2 and 7.6 for detailed discussion of the safety and efficacy of oteseconazole in this study). Oteseconazole plasma PK parameters associated with the induction dosing regimen are summarized in Table 142. Mean Day 14, Week 14 and Week 50 plasma concentrations were 1.40 µg/mL, 2.68 µg/mL and 0.87 µg/mL, respectively.

Table 142. Summary of Oteseconazole Noncompartmental Pharmacokinetic Parameters by Treatment and Day

Treatment, Day Statistic	Pharmacokinetic Parameter						
	C _{max} (µg/L)	t _{max} (h)	AUC _{last} (h*µg/L)	AUC _{0,24} (h*µg/L)	AUC _{0,8} (h*µg/L)	t _{last} (h)	C _{last} (µg/L)
Oteseconazole 4x150 mg, Day 1							
N	10	10	10	8	10	10	10
Mean (SD)	1750 (751)	NC (NC)	21500 (7910)	21600 (7790)	8100 (3100)	NC (NC)	698 (264)
CV%	42.9	NC	36.8	36.0	38.3	NC	37.9
Geometric Mean	1620	NC	20300	20600	7570	NC	651
Geometric CV%	42.2	NC	36.3	33.9	41.0	NC	41.5
Median (Min, Max)	1520 (995, 3130)	4.01 (2.00, 18.00)	20800 (12700, 38200)	20800 (13400, 38200)	7980 (3730, 14000)	22.70 (18.00, 23.87)	716 (354, 1150)
Oteseconazole 3x150 mg, Day 2							
N	10	10	10	NC	10	10	10
Mean (SD)	2080 (562)	NC (NC)	12100 (3190)	NC (NC)	12100 (3130)	NC (NC)	1560 (393)
CV%	27.1	NC	26.4	NC	26.0	NC	25.2
Geometric Mean	2010	NC	11700	NC	11700	NC	1510
Geometric CV%	27.7	NC	25.9	NC	25.5	NC	28.8
Median (Min, Max)	2100 (1360, 3150)	4.00 (2.00, 8.00)	11500 (8150, 17700)	NC	11500 (8150, 17400)	8.00 (7.92, 8.17)	1650 (836, 2010)

Abbreviations: AUC_{0,8}=area under the plasma concentration-time curve from time 0 to 8 hours; AUC_{0,24}=area under the plasma concentration-time curve from time 0 to 24 hours; C_{last}=last observed quantifiable concentration; C_{max}=maximum observed concentration; CV%=arithmetic percent coefficient of variation; Geometric CV%=geometric percent coefficient of variation; Max=maximum; Mean=arithmetic mean; Min=minimum; N=sample size; NC=not calculated; SD=standard deviation; t_{last}=observed time of last quantifiable concentration; t_{max}=time of maximum observed concentration.

Note: AUC_{0,24} was not reported for Day 2 because samples were collected only up to 8 hours.

Note: No extrapolations were carried out for the estimation of partial areas because $t_{1/2}$ could not be estimated on both days.

Note: The AUC_{last} was substituted for AUC_{0,24} when t_{last} was <24 hours and the percentage difference between t_{last} and 24 hours was <10%. The AUC_{last} was substituted for AUC_{0,8} when t_{last} was <8 hours and the percentage difference between t_{last} and 8 hours was <10%.

Data source: Report CL-017-PK Table 9-2 and Section 16.7

The Applicant explored the relationship between quartiles of Day 14 exposure from studies CL-011, CL-012 and CL-017 and recurrence of acute VVC in the safety and maintenance phase ITT population. To this end, the Applicant performed a logistic regression analysis on the proportion of subjects who experienced ≥ 1 episode of culture verified acute VVC during the maintenance phase and estimated the hazard ratio for the time to recurrence. The overall hazard ratio for time to recurrence was low across oteseconazole exposure quartiles, ranging from 0.03 to 0.17. Statistically, the proportion of subjects treated with oteseconazole (regardless of Day 14 exposure) who experienced a recurrence of VVC infection was lower than the proportion of subjects treated with fluconazole + placebo (designated as BLQ group) who experienced recurrence in the maintenance phase (Table 143).

Table 143. Logistic Regression for the Proportion of Subjects With ≥ 1 Culture-Verified Acute VVC Episodes During the Maintenance Phase

	Parameter Estimate (Std. Error)	Parameter Estimate 95% CI	p-value	Odds Ratio (95% CI)	Global Test p-value (Min, Max)
One or more culture-verified acute VVC episodes (Missing value imputed with MI) [1]					<0.001 (<0.001, <0.001)
Intercept	-0.111 (0.298)	-0.694, 0.473	0.710		
Oteseconazole Concentration Bin			<0.001		
Bin - (0, 1080] vs. BLQ	-1.918 (0.349)	-2.602, -1.234	<0.001	0.147 (0.074, 0.291)	
Bin - (1080, 1670] vs. BLQ	-2.521 (0.434)	-3.371, -1.671	<0.001	0.080 (0.034, 0.188)	
Bin - (1670, 2200] vs. BLQ	-3.646 (0.724)	-5.066, -2.226	<0.001	0.026 (0.006, 0.108)	
Bin - (2200, 4260] vs. BLQ	-2.968 (0.527)	-4.002, -1.934	<0.001	0.051 (0.018, 0.145)	
Screening signs and symptoms score	-0.039 (0.031)	-0.099, 0.021	0.208	0.962 (0.906, 1.022)	

Source: Table ISE.26.2 of Applicant's Summary of Clinical Efficacy
Abbreviations: BLQ, below the limit quantification; MI, multiple imputations; VVC, vulvovaginal candidiasis

14.3. Pharmacometrics Review

In general, the Applicant's population PK analysis is considered acceptable in capturing oteseconazole's PK. More specifically, the developed model was used to support the current submission as outlined below:

Table 144. Utility of the Population PK Model

Utility of the final model	Reviewer's Comments
Derive exposure metrics and PK parameters - The popPK was used to assess the adequacy of the proposed fixed dosing in all patients from adolescents to adults. - The popPK model was used to predict oteseconazole maximum and minimum concentrations (C_{max} and C_{min}) and the area under the concentration-time curve over the dosing interval (AUC_T) after each dose, as well as predict oteseconazole half-life.	- PK simulations shows that at lower body weights ranging from 29 to <40 kg (expected to be most prevalent in younger adolescent population < 16 years old), the median AUC_T, median C_{max}, and median C_{min} is about 2-fold the median values observed in patients with body weight ranging from 60 to 70 kg (Figure 15 and Figure 16). - The clinical studies did not include adolescent patients younger than 16 years old (3 patients with age 16 to 17 years old). No treatment-emergent adverse events (TEAEs) were observed in these patients. Only one patient weighing <40 kg was enrolled in the Phase 3 studies (VMT-VT-1161-CL-011, VMT-VT-1161-CL-012, VMT-VT-1161-CL-017), and patients weighing between 40 to 59 kg did not have increased AEs compared to those weighing at least 60 kg. Therefore, given the favorable safety profile of oteseconazole, no dose adjustment based on body weight is warranted in adolescent patients.

Source: Reviewer
Abbreviations: AEs, adverse events; AUC_T , area under the curve during a dosing interval; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; PopPK, population pharmacokinetics.

14.3.1. Applicant's Population PK Analysis

The population pharmacokinetic (popPK) analysis was based on PK data from 8 studies ([Table 145](#)): four Phase 1 studies in healthy subjects and four Phase 2 studies in different patients' populations with interdigital tinea pedis (VMT-VT-1161-CL-003), toenail onychomycosis

(VMT-VT-1161-CL-005), and acute or recurrent vulvovaginal candidiasis (VMT-VT-1161-CL-004 and VMT-VT-1161-CL-006).

Oteseconazole (or VT-1161) was administered orally as single and multiple doses of 5 to 600 mg through 24 weeks ([Table 145](#)), either under fasted condition, with a high-fat breakfast or regular meal ([Table 146](#)), and either as capsules (VMT-VT-1161-CL-001 and VMT-VT-1161-CL-002), over-encapsulated tablets (VMT-VT-1161-CL-003 and VMT-VT-1161-CL-004) or tablets without over-encapsulation ([Table 146](#)).

The analysis dataset was comprised of 8033 PK observations from 604 subjects, including 496 BLQ (below limit of quantification: 20 ng/mL) concentrations. Among the 604 subjects, 17 subjects had all their sampled PK observations as BLQ: all 9 subjects from study VMT-VT-1161-CL-001 at dose levels 5 and 10 mg, 7 patients from study VMT-VT-1161-CL-005 and 1 patient from study VMT-VT-1161-CL-006. All BLQ observations were kept in the analysis dataset and were handled using the M3 method during the popPK analysis.

The summary statistics for the continuous and categorical covariates are presented by study in [Table 146](#) (individuals in which all PK observations were BLQ were discarded for the summary). A total of 203 adult patients with acute vulvovaginal candidiasis and recurrent vulvovaginal candidiasis were available for the popPK analysis.

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Table 145. Oteseconazole Clinical Studies Used for the Population Pharmacokinetic Analysis

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample Collection
VMT-VT-1161-CL-001	Healthy volunteers	Phase 1, single-center, randomized, double-blind, placebo-controlled, escalating single dose study of VT-1161 in healthy adult subjects	Cohort 1: 5 mg single dose VT-1161 or placebo with fasting Cohort 2: 10 mg single dose VT-1161 or placebo with fasting Cohort 3: 20 mg single dose VT-1161 or placebo with fasting Cohort 4: 40 mg single dose VT-1161 or placebo with fasting Cohort 5: 80 mg single dose VT-1161 or placebo with fasting Cohort 6: 160 mg single dose VT-1161 or placebo with fasting Cohort 7: 320 mg single dose VT-1161 or placebo with fasting Cohort 8: 320 mg VT-1161 or placebo with high fat meal	Cohorts 1-6: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 144, 312 hours after single dose Cohorts 7 and 8: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 144, 312, 648, 984 hours after dosing
VMT-VT-1161-CL-002	Healthy volunteers	Phase 1, single-center, randomized, double-blind, placebo-controlled, escalating multiple-dose study of VT-1161 in healthy adult subjects	Cohort 1: 40 mg VT-1161 or placebo QAM with high fat meal for 7 days Cohort 2: 80 mg VT-1161 or placebo QAM with high fat meal for 7 days Cohort 3: 160 mg VT-1161 or placebo QAM with high fat meal for 7 days Cohort 4: 320 mg VT-1161 or placebo QAM with high fat meal for 7 days	For all cohorts: Day 1: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, and 16 hours post-dose Days 2-6: Pre-dose

NDA 215888
Vivjoa (oteseconazole)

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample Collection
				Day 7: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 60, and 72 hours following the last dose of study drug Days 14, 21, 28, 35, 49: Once daily in the morning at each visit
VMT-VT-1161-CL-003	Volunteers with moderate to severe interdigital tinea pedis	Phase 2a, multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of oral VT-1161 over-encapsulated tablets	Cohort 1: placebo Cohort 2: 200 mg VT-1161 QD for 4 days, then 50 mg QD for 10 days Cohort 3: 600 mg VT-1161 QD for 4 days, then 150 mg QD for 10 days Cohort 4: 600 mg VT-1161 BID for 4 days, then 300 mg QD for 10 days or placebo	For all cohorts: Day 1 (consenting patients only): Pre-dose, 1, 2, 3, 4, 5, 6, and 8 hours post-dose Day 7: pre-dose Day 14 (consenting patients only): Pre-dose, 1, 2, 3, 4, 5, 6, and 8 hours post-dose Days 28, 42, 84, and 168 post-dose

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample Collection
VMT-VT-1161-CL-004	Volunteers with moderate to severe acute vulvovaginal candidiasis	Phase 2a, multi-center, randomized, double-blind, active-controlled, parallel-group, dose ranging study of oral VT-1161 over-encapsulated tablets compared to fluconazole	Cohort 1: 300 mg VT-1161 QD for 3 days Cohort 2: 600 mg VT-1161 QD for 3 days Cohort 3: 150 mg fluconazole for 3 days Cohort 4: 600 mg BID VT-1161 or fluconazole for 3 days	For all cohorts: Day 1: pre-dose Day 1 (consenting patients only): pre-dose, 1, 2, 3, 4, 5, 6, 8 hours post-dose Days 7, 14, 28, 84, 168: pre-dose
VMT-VT-1161-CL-005	Volunteers with toenail onychomycosis	Phase 2, multi-center, randomized, double-blinded, active-controlled, parallel-group dose-ranging study of oral VT-1161 tablets	Cohort 1: 300 mg VT-1161 QD for 2 weeks, then 300 mg VT-1161 QW for 10 weeks, then placebo QW for 12 weeks Cohort 2: 600 mg VT-1161 QD for 2 weeks, then 600 mg VT-1161 QW for 10 weeks, then placebo QW for 12 weeks Cohort 3: 300 mg VT-1161 QD for 2 weeks, then 300 mg VT-1161 QW for 22 weeks Cohort 4: 600 mg VT-1161 QD for 2 weeks, then 600 mg VT-1161 QW for 22 weeks Cohort 5: matching placebo for 24 weeks	For all cohorts: Week 0: pre-dose Day 14: pre-dose Day 14 (consenting patients only): pre-dose, 1, 2, 3, 4, 5, 6, 8 hours post-dose Follow-up visits on Weeks 4, 8, 12, 18, 24, 36, 48, 60

NDA 215888
Vivjoa (oteseconazole)

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample Collection
VMT-VT-1161-CL-006	Volunteers with recurrent vulvovaginal candidiasis	Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of oral VT-1161	Induction phase: 3 sequential 150 mg fluconazole Q72H Cohort 1: 150 mg VT-1161 for 12 weeks, then placebo for 12 weeks Cohort 2: 150 mg VT-1161 for 24 weeks Cohort 3: 300 mg VT-1161 for 12 weeks, then placebo for 12 weeks Cohort 4: 300 mg VT-1161 for 24 weeks Cohort 5: placebo for 24 weeks All cohorts: loading dose QD for 7 days, then maintenance dose QW for remainder of 24 weeks	For all cohorts: Day 7, Weeks 4, 8, 12, 18, 24, 36, 48 Day 7 (consenting patients only): pre-dose, 1, 2, 3, 4, 5, 6, 8 hours post-dose
VMT-VT-1161-CL-007	Healthy volunteers	Phase 1, single-center, open-label, drug-drug interaction (DDI) single and multiple oral dose study of VT-1161 on PK of single doses of midazolam and Pharmacokinetic Evaluation (PKE) of alternate strength tablet	DDI Cohort: single 2 mg midazolam on Day 1, followed by 600 mg VT-1161 QD from Days 3-16 with single 2 mg midazolam on Day 3 and Day 16 PKE Cohort: single 600 mg dose VT-1161	DDI Cohort: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 hours post-Day 1 (midazolam only), post-Day 3, and post-Day 16 doses Day 5-15: pre-dose PKE Cohort: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 hours post-Day 1 dose

NDA 215888
 Vivjoa (oteseconazole)

Study #	Patient Population	Study Design	Dose and Dosing Regimen	Blood Sample Collection
VMT-VT-1161-CL-008	Healthy Japanese and Western volunteers	Phase 1, open-label multiple dose study of oral VT-1161	Cohort 1: 300 mg VT-1161 QD for 14 days, Japanese subjects only Cohort 2: 300 mg VT-1161 QD for 14 days, Western subjects only Cohort 3: 600 mg VT-1161 QD for 14 days, Japanese subjects only Cohort 4: 600 mg VT-1161 QD for 14 days, Western subjects only	Day 1-7: pre-dose Day 14: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, 60, 72 hours post-dose Day 28 follow-up visit

Source: Applicant's Population PK Report, Appendix 1, pages 102-106.
 Abbreviations: BID, twice daily; QAM, every morning; QD, daily

Table 146. Summary of Baseline Demographic Characteristics

	CL-001 (N=39)	CL-002 (N=24)	CL-003 (N=38)	CL-004 (N=40)	CL-005 (N=197)	CL-006 (N=163)	CL-007 (N=35)	CL-008 (N=51)	All studies (N=587)
Age (years)									
Mean (SD)	36.8 (8.74)	43.3 (7.98)	40.1 (12.8)	33.2 (11.2)	49.8 (10.5)	34.5 (9.60)	40.9 (10.0)	36.5 (10.4)	41.0 (12.2)
Median [Min, Max]	39.0 [22.0, 55.0]	44.5 [25.0, 54.0]	41.5 [19.0, 66.0]	30.0 [18.0, 60.0]	51.0 [22.0, 70.0]	33.0 [18.0, 58.0]	44.0 [25.0, 55.0]	35.0 [19.0, 55.0]	41.0 [18.0, 70.0]
Weight (kg)									
Mean (SD)	80.0 (13.3)	81.1 (10.7)	95.8 (19.0)	72.1 (17.9)	93.3 (20.4)	72.4 (19.1)	79.1 (13.3)	68.9 (12.8)	81.9 (20.7)
Median [Min, Max]	79.1 [60.0, 107]	81.4 [61.0, 108]	93.7 [60.3, 134]	67.6 [43.5, 118]	90.0 [51.1, 193]	68.0 [43.1, 151]	81.8 [55.5, 106]	64.9 [42.3, 98.2]	79.2 [42.3, 193]
BMI (kg/m²)									
Mean (SD)	26.6 (2.45)	28.4 (2.44)	31.4 (7.11)	27.6 (6.65)	30.2 (5.88)	27.1 (6.65)	26.5 (3.29)	24.4 (2.97)	28.2 (5.99)
Median [Min, Max]	27.2 [21.4, 30.1]	29.0 [21.1, 31.9]	30.8 [19.9, 45.5]	25.4 [17.7, 47.6]	29.0 [19.4, 54.6]	25.2 [17.2, 47.6]	26.6 [19.0, 31.5]	24.1 [18.3, 31.9]	27.2 [17.2, 54.6]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	1 (0.2%)
eGFR (mL/min/1.73m²)									
Mean (SD)	88.3 (12.7)	98.1 (18.6)	88.5 (20.7)	105 (22.5)	85.2 (15.8)	96.8 (19.2)	95.6 (19.0)	101 (30.3)	92.8 (20.4)
Median [Min, Max]	89.0 [62.0, 125]	103 [68.0, 127]	86.5 [59.0, 138]	100 [57.0, 162]	85.0 [46.0, 133]	96.0 [50.0, 176]	90.0 [66.0, 136]	100 [66.0, 258]	90.0 [46.0, 258]
Total Bilirubin (mg/dL)									
Mean (SD)	0.505 (0.254)	0.446 (0.174)	0.497 (0.194)	0.483 (0.200)	0.581 (0.303)	0.471 (0.217)	0.551 (0.422)	0.522 (0.248)	0.521 (0.268)
Median [Min, Max]	0.400 [0.200, 1.30]	0.400 [0.200, 0.800]	0.500 [0.200, 0.900]	0.450 [0.200, 1.00]	0.500 [0.100, 2.00]	0.400 [0.100, 1.40]	0.500 [0.100, 2.70]	0.500 [0.200, 1.20]	0.500 [0.100, 2.70]
Direct Bilirubin (mg/dL)									
Mean (SD)	0.156 (0.0788)	0.0858 (0.0280)	0.168 (0.0702)	0.168 (0.0616)	0.169 (0.0796)	0.145 (0.0695)	0.131 (0.0676)	0.165 (0.0658)	0.155 (0.0738)
Median [Min, Max]	0.100 [0.100, 0.400]	0.0800 [0.0400, 0.130]	0.200 [0.100, 0.400]	0.200 [0.100, 0.300]	0.200 [0.100, 0.500]	0.100 [0.100, 0.400]	0.100 [0, 0.400]	0.200 [0.100, 0.300]	0.100 [0, 0.500]
Indirect Bilirubin (mg/dL)									
Mean (SD)	0.349 (0.189)	0.360 (0.149)	0.329 (0.139)	0.315 (0.151)	0.412 (0.236)	0.326 (0.162)	0.420 (0.368)	0.357 (0.189)	0.365 (0.211)
Median [Min, Max]	0.300 [0.100, 1.00]	0.320 [0.150, 0.680]	0.300 [0.100, 0.600]	0.300 [0.100, 0.700]	0.400 [0, 1.50]	0.300 [0, 1.00]	0.300 [0.100, 2.30]	0.300 [0.100, 0.900]	0.300 [0, 2.30]
Albumin (g/dL)									
Mean (SD)	4.54 (0.289)	4.23 (0.186)	4.37 (0.204)	4.37 (0.292)	4.42 (0.272)	4.40 (0.252)	4.36 (0.329)	4.50 (0.302)	4.41 (0.274)
Median [Min, Max]	4.50 [3.80, 5.20]	4.30 [3.80, 4.60]	4.40 [4.00, 5.00]	4.40 [3.70, 5.30]	4.40 [3.50, 5.10]	4.40 [3.70, 5.10]	4.30 [3.70, 5.10]	4.50 [3.70, 5.20]	4.40 [3.50, 5.30]

NDA 215888
Vivjoa (oteseconazole)

	CL-001 (N=39)	CL-002 (N=24)	CL-003 (N=38)	CL-004 (N=40)	CL-005 (N=197)	CL-006 (N=163)	CL-007 (N=35)	CL-008 (N=51)	All studies (N=587)
BMI groups									
Underweight	0 (0%)	0 (0%)	0 (0%)	2 (5.0%)	0 (0%)	4 (2.5%)	0 (0%)	1 (2.0%)	7 (1.2%)
Normal	11 (28.2%)	2 (8.3%)	7 (18.4%)	16 (40.0%)	32 (16.2%)	72 (44.2%)	9 (25.7%)	34 (66.7%)	183 (31.2%)
Overweight	27 (69.2%)	16 (66.7%)	12 (31.6%)	11 (27.5%)	80 (40.6%)	47 (28.8%)	20 (57.1%)	12 (23.5%)	225 (38.3%)
Obese	1 (2.6%)	6 (25.0%)	19 (50.0%)	11 (27.5%)	85 (43.1%)	39 (23.9%)	6 (17.1%)	4 (7.8%)	171 (29.1%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)	0 (0%)	1 (0.2%)
CKD stages									
Normal	19 (48.7%)	16 (66.7%)	18 (47.4%)	31 (77.5%)	70 (35.5%)	97 (59.5%)	21 (60.0%)	32 (62.7%)	304 (51.8%)
Mild	20 (51.3%)	8 (33.3%)	19 (50.0%)	8 (20.0%)	122 (61.9%)	64 (39.3%)	14 (40.0%)	19 (37.3%)	274 (46.7%)
Mild to moderate	0 (0%)	0 (0%)	1 (2.6%)	1 (2.5%)	5 (2.5%)	2 (1.2%)	0 (0%)	0 (0%)	9 (1.5%)
Total Bilirubin levels									
above UNL* (> 1.2 mg/dL)	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	9 (4.6%)	2 (1.2%)	1 (2.9%)	0 (0%)	13 (2.2%)
below LNL* (< 0.3 mg/dL)	2 (5.1%)	2 (8.3%)	3 (7.9%)	3 (7.5%)	9 (4.6%)	16 (9.8%)	2 (5.7%)	5 (9.8%)	42 (7.2%)
Normal	36 (92.3%)	22 (91.7%)	35 (92.1%)	37 (92.5%)	179 (90.9%)	145 (89.0%)	32 (91.4%)	46 (90.2%)	532 (90.6%)
Direct Bilirubin levels									
Normal	38 (97.4%)	24 (100%)	37 (97.4%)	40 (100%)	190 (96.4%)	159 (97.5%)	34 (97.1%)	51 (100%)	573 (97.6%)
above UNL* (> 0.3 mg/dL)	1 (2.6%)	0 (0%)	1 (2.6%)	0 (0%)	7 (3.6%)	4 (2.5%)	1 (2.9%)	0 (0%)	14 (2.4%)

NDA 215888
Vivjoa (oteseconazole)

Gender									
Male	27 (69.2%)	17 (70.8%)	30 (78.9%)	0 (0%)	157 (79.7%)	0 (0%)	24 (68.6%)	25 (49.0%)	280 (47.7%)
Female	12 (30.8%)	7 (29.2%)	8 (21.1%)	40 (100%)	40 (20.3%)	163 (100%)	11 (31.4%)	26 (51.0%)	307 (52.3%)
Race									
White	22 (56.4%)	20 (83.3%)	25 (65.8%)	20 (50.0%)	168 (85.3%)	94 (57.7%)	6 (17.1%)	14 (27.5%)	369 (62.9%)
Black/Afr.Amer	15 (38.5%)	4 (16.7%)	13 (34.2%)	19 (47.5%)	28 (14.2%)	63 (38.7%)	26 (74.3%)	12 (23.5%)	180 (30.7%)
Asian	0 (0%)	0 (0%)	0 (0%)	1 (2.5%)	0 (0%)	4 (2.5%)	0 (0%)	25 (49.0%)	30 (5.1%)
Amer.Ind./Alaska Native	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	1 (2.9%)	0 (0%)	3 (0.5%)
Hawaii./Pacif.Island.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
multiple	1 (2.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.2%)	2 (5.7%)	0 (0%)	5 (0.9%)
Ethnicity									
Not hispanic/Latino	28 (71.8%)	5 (20.8%)	34 (89.5%)	34 (85.0%)	176 (89.3%)	136 (83.4%)	30 (85.7%)	47 (92.2%)	490 (83.5%)
Hispanic/Latino	11 (28.2%)	19 (79.2%)	4 (10.5%)	6 (15.0%)	15 (7.6%)	27 (16.6%)	5 (14.3%)	4 (7.8%)	91 (15.5%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (3.0%)	0 (0%)	0 (0%)	0 (0%)	6 (1.0%)
Meal type									
Fasted	33 (84.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	33 (5.6%)
Regular meal	0 (0%)	0 (0%)	38 (100%)	40 (100%)	197 (100%)	0 (0%)	0 (0%)	51 (100%)	326 (55.5%)
High-fat meal	6 (15.4%)	24 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (100%)	0 (0%)	65 (11.1%)
unspecified meal type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	163 (100%)	0 (0%)	0 (0%)	163 (27.8%)
Formulation									
Capsules	39 (100%)	24 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	63 (10.7%)
Tablets over-encapsulated	0 (0%)	0 (0%)	38 (100%)	40 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	78 (13.3%)
Tablets	0 (0%)	0 (0%)	0 (0%)	0 (0%)	197 (100%)	163 (100%)	35 (100%)	51 (100%)	446 (76.0%)

Source: Reviewer's Summary from the Population PK datasets.

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; LNL: laboratory lower normal limit; UNL: laboratory upper normal limit.

Base PK model

The pharmacokinetics of oteseconazole was best described by a 2-compartment distribution model with linear elimination from the central compartment. Absorption was characterized as first-order with a lag time. The PK model was parameterized in terms of apparent clearance (CL/F), apparent central and peripheral volumes of distribution (V2/F and V3/F respectively), apparent intercompartmental clearance (Q/F), absorption rate constant (Ka) and absorption lag time. Between subject variability was estimated on CL/F, V2/F, V3/F and Ka. The residual error model consisted of a combined additive and proportional error model.

Covariates Analysis

Age, gender, race, body weight, body mass index (BMI), health status (healthy volunteer, VVC, onychomycosis), diet (fasted, regular, or high-fat meal), formulation (capsules, over-encapsulated tablets, tablets without over-encapsulation), total bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), estimated glomerular filtration (using the modification of diet in renal disease [MDRD] formula) were the examined covariates during covariate model selection.

The following covariates were included in the final model:

- Body Weight (time varying covariate) on CL/F, Q/F, V2/F and V3/F using a power model, centered at 70 kg
- Race (white versus all other groups) on CL/F (using an exponential model)
- Total Bilirubin (time varying covariate) on CL/F using a power model, centered at a median total serum bilirubin level of 0.5 mg/dL
- Albumin (time varying covariate) on V2/F using a power model, centered at a median albumin level of 4.4 g/dL
- Formulation (capsules and non-over-encapsulated tablets) on the relative oral bioavailability (F1)
- Study VMT-VT-1161-CL-002 on V2/F (using an exponential model)
- Study VMT-VT-1161-CL-007 on Ka (using an exponential model)

Final Model

The parameter estimates from the final popPK model for oteseconazole are listed in [Table 147](#). According to the popPK model, an average 70 kg white individual with a normal total bilirubin level of 0.5 mg/dL, normal albumin level of 4.4 g/dL, and receiving the capsules formulation, the population estimates for oteseconazole CL/F, V2/F, Q/F, V3/F, F1, Ka and absorption lag time are 0.253 L/h (6.07 L/day), 423 L, 44.5 L/h, 894 L, 1.9 (i.e., 90% higher bioavailability compared to over-encapsulated tablets), 0.278 h⁻¹ and 0.956 h. The estimated interindividual or between subject variability expressed as coefficient of variation (%CV) was 155%, 53%, 56% and 334% for CL/F, V2/F, V3/F, and Ka, respectively. The interindividual random effect (ETA) shrinkage from the final popPK model was 14.8%, 42.3%, 16.6%, and 43.3% for CL/F, V2/F, V3/F, and Ka.

Table 147. Parameter Estimates From the Final Population PK Model

Parameter (units)	NONMEM parameter	Estimate	Relative Standard Error
CL/F (L/h)	THETA(1)	0.253	8.38
V2/F (L)	THETA(2)	423	5.25
V3/F (L)	THETA(3)	894	4.37
KA (1/h)	THETA(4)	0.278	17.34
Q (L/h)	THETA(5)	44.5	2.29
Additive residual error term (ng/ml)	THETA(6)	61.5	0.826
Proportional residual error term	THETA(7)	12	0.378
Lag time (h)	THETA(8)	0.956	0.331
Effect of VMT-VT-1161-CL-002 on central volume of distribution (Exponential model)	THETA(9)	-0.636	27.0
Effect of capsules and non-over encapsulated tablets on F1	THETA(10)	1.9	2.25
Weight effect on volume of distribution (Power model)	THETA(11)	1.43	4.97
Effect of VMT-VT-1161-CL-007 on Ka (Exponential model)	THETA(12)	1.2	29.3
Effect of serum bilirubin on clearance (Power model)	THETA(13)	-0.125	3.10
Effect of race (non-Caucasian) on clearance (Exponential model)	THETA(14)	0.394	25.6
Effect of albumin on central volume of distribution (Power model)	THETA(15)	-0.742	1.79

	OMEGA (n,1) Clearance	OMEGA (n,2) Central Volume of Distribution	OMEGA (n,3) Peripheral Volume of Distribution	OMEGA (n,4) Ka
OMEGA (1,n)	1.22	NA	NA	NA
OMEGA (2,n)	NA	0.251	NA	NA
OMEGA (3,n)	NA	NA	0.271	NA
OMEGA (4,n)	NA	NA	NA	2.5

Source: Applicant's Population PK Report, Table 7 and 8, page 21.

Abbreviations: CL/F, apparent clearance; h, hour; KA, first-order absorption rate constant; PK, pharmacokinetic; Q, flow rate; V2/F, central volume of distribution; V3/F, peripheral volume of distribution.

Reviewer's Comment: In [Table 147](#), the correct percent relative residual error (%RSE) from the Applicant's final model is 31% for THETA(13) and 17.9% for THETA(15), instead of 3.1% and 1.79%, respectively.

Body weight was found to be an important covariate on CL/F and Q/F (allometric exponent fixed to 0.75), as well as on the apparent volumes of distribution with an estimated allometric exponent for V2/F and V3/F of 1.43. The estimated value is larger than the theoretical value of

1.0, and the physiological reason for this deviation from the theoretical value is unknown. According to the Applicant, the clinical implications are likely limited, as the long half-life of oteseconazole (4126 h) results in a very small peak to trough ratio.

Two studies that used the over-encapsulated tablets formulation (studies VMT-VT-1161-CL-003 and VMT-VT-1161-CL-004) showed 90% lower bioavailability. According to the Applicant, the lower F1 for the over-encapsulated tablets formulation could be partly attributed to the nonstandardized caloric content of the meals taken prior to dosing ([Table 146](#)).

An effect of race was found on CL/F, with non-Caucasian subjects having 48% higher clearance than Caucasian subjects. The majority of non-Caucasian subjects were African American (about 82%, [Table 146](#)). According to the Applicant, the reason for this effect is unknown, but the effect was moderate in size and is unlikely to have clinical implications.

Total bilirubin was found to be negatively correlated with clearance, with an estimated average effect of about 13% lower CL/F for a total bilirubin level of 1.5 mg/dL (median of observed total bilirubin levels > 1.2 mg/dL), and about 19% lower CL/F for the highest observed total bilirubin level of 2.7 mg/dL. Based on an information request (see Section [14.3.3](#)), 49 subjects reported total bilirubin values above normal. The vast majority were mild, occurred on a single occasion and had resolved at the subsequent visit. Total bilirubin increases were balanced between subject receiving oteseconazole and placebo. Most reported total bilirubin increases were in study VT-1161-CL-005 ([Table 146](#)), in which 11 subjects were identified with 3 or more consecutive high total bilirubin values, and 8 of the 11 subjects had a normal total bilirubin value at their last study visit. In most cases increases in total bilirubin were associated with increases in both direct and indirect bilirubin. For most subjects, no obvious association between increased total bilirubin and underlying medical condition or concomitant medications can be made. In a revised population PK analysis, the Applicant evaluated the relationship between direct bilirubin as well as indirect bilirubin levels (as a time varying continuous variable) and oteseconazole CL/F, in order to determine whether total bilirubin, indirect bilirubin, or direct bilirubin is the best predictor of clearance. The revised popPK model with direct bilirubin as a covariate on CL/F provided a better fit (lower objective function value [OFV]) compared to the original final popPK model (i.e., with total bilirubin as covariate on CL/F, see [Table 147](#)). In the revised popPK model all the PK parameters remained comparable to the original model, with the exception of the estimated effect of direct bilirubin on CL/F. According to the revised model, direct (conjugated) bilirubin was found to be negatively correlated with CL/F, with an estimated 22% lower CL/F for a direct bilirubin level of 0.4 mg/dL (median of observed direct bilirubin levels > 0.3 mg/dL), and about 34 % lower CL/F for the highest observed direct bilirubin level of 0.6 mg/dL.

Serum albumin was negatively correlated with the apparent central volume of distribution V2/F, with an estimated 24% higher V2/F for the lowest observed albumin level of 3.3 g/dL, an estimated 13% lower V2/F for the highest observed albumin level of 5.3 g/dL. However, all enrolled subjects had normal serum albumin levels.

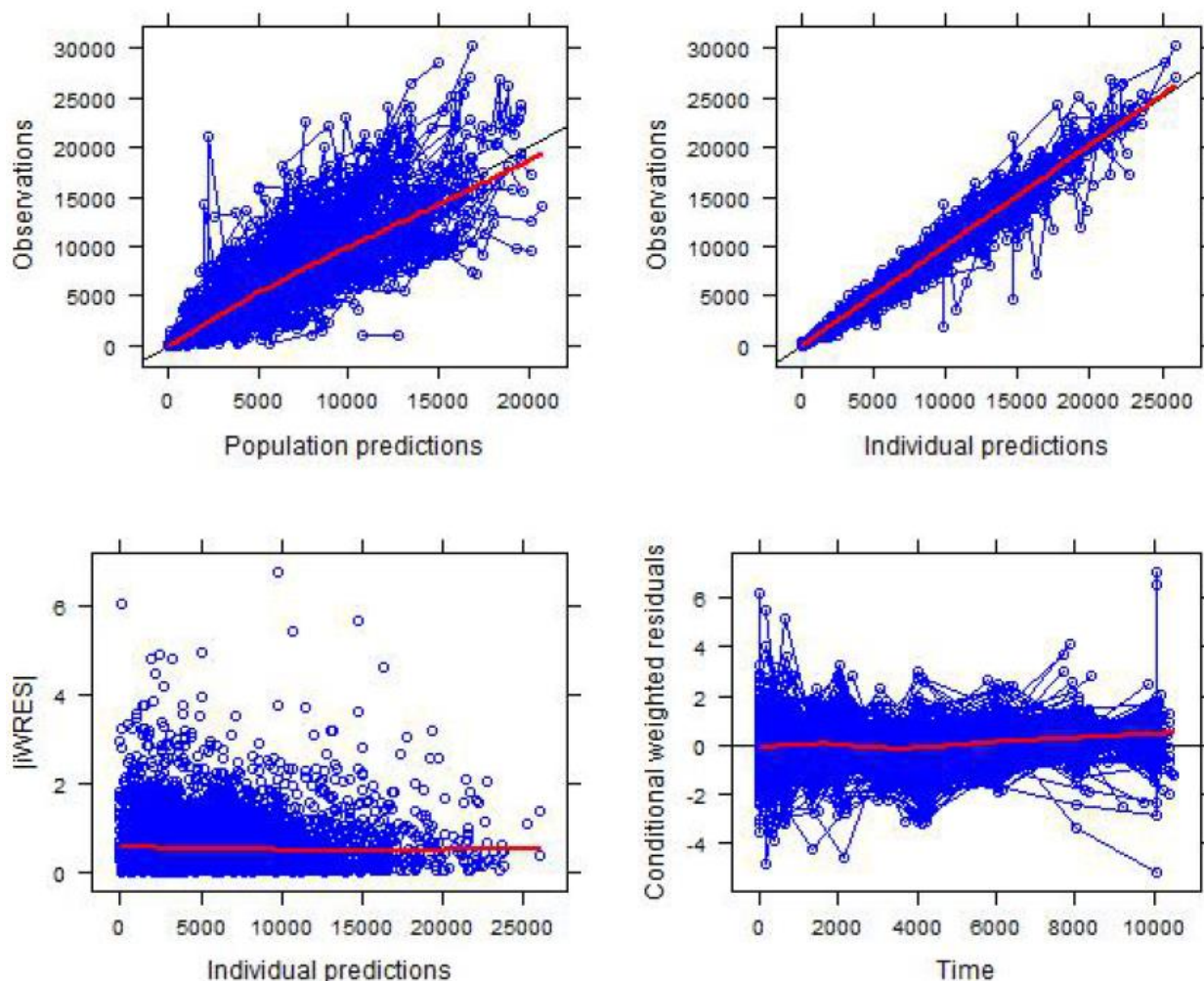
According to the popPK model, subjects in study VMT-VT-1161-CL-002 were estimated to have 47% lower V2/F compared to the other studies. This study was in healthy adult subjects receiving oteseconazole after ingestion of a high-fat meal. High-fat meals are expected to influence oteseconazole bioavailability, which according to the popPK model parameterization should also be reflected in the apparent clearance CL/F. However, a trend of higher CL/F was observed from the covariate plots between study VMT-VT-1161-CL-002 and CL/F. According

to the Applicant, no clear explanation was found for this observation, and this effect likely has no clinical implications given the long half-life and the small peak to trough ratio of oteseconazole. Besides, no relationship was observed between diet and CL/F or V2/F.

According to the popPK model, study VMT-VT-1161-CL-007 was found to have a larger value for K_a (3.3 folds higher, i.e., more rapid absorption) than the other studies. No clear explanation was found for this. According to the Applicant, this effect likely has no clinical implications given the long half-life and therefore the small peak to trough range of VT-1161.

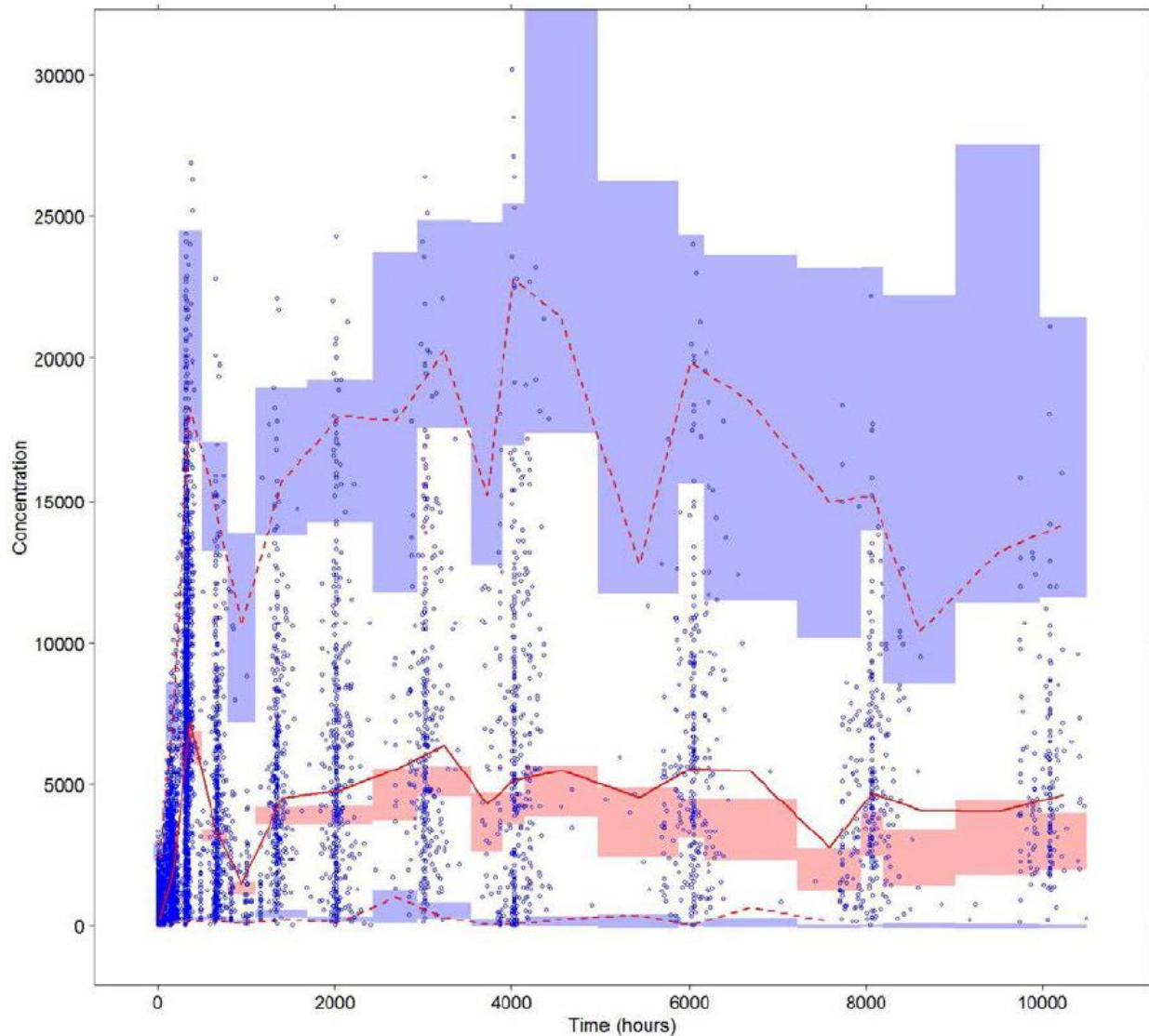
The goodness-of-fit (GOF) plots from the final popPK model, are shown in [Figure 13](#). The plots of the observed concentrations versus population predicted as well as the individual predicted concentrations show random normal scatter around the identity lines, indicating absence of systematic bias. The population conditional and individual weighted residuals versus time after dose or versus population predicted concentrations also show random normal scatter around zero with no specific trend, indicating no major model misspecifications. The Visual Predictive Check (VPC) plots ([Figure 14](#)) of concentrations versus time showed a reasonable agreement between the observed and simulated data.

Figure 13. Goodness of Fit Plots From the Final PK Model



Source: Applicant's Population PK Report, Figure 48, page 71.
Abbreviations: PK, pharmacokinetic.

Figure 14. Visual Predictive Check for the Final PK Model



Source: Applicant's Population PK Report, Figure 50, page 73.
Abbreviations: PK, pharmacokinetic.

14.3.2. Reviewer's Assessment of the Population PK Analysis

Assessment of the Covariate Analysis

- The Applicant's PK model reasonably describes the observed concentrations from oteseconazole clinical studies.
- The PK parameters from the final model were estimated with acceptable precision, with a %RSE ranging between 0.3 % and 31%.
- Among the PK parameters that are affected by the identified covariates, the ETA shrinkage was relatively high for V2/F (42.3%) and Ka (42.3%), which makes the graphical assessment of covariate on these parameters less reliable.

- A backward deletion of each covariate from the Applicant's popPK model, found that total bilirubin levels was not a statistically significant covariate on CL/F (at a significance level of 0.001), with a change in the OFV by 8 points after removal of the covariate. In addition, the evaluation of total bilirubin as a categorical variable on CL/F did not decrease the OFV compared to a reduced model without total bilirubin as covariate (1 point drop in OFV for 1 degree of freedom [df]).

According to our evaluation of the revised popK model from the Applicant, the use of direct bilirubin instead of total bilirubin (as covariate on CL/F) did not improve the model fit as reported by the Applicant, yielding comparable OFV between the revised popPK model and the original model (which used total bilirubin as covariate). The evaluation of direct bilirubin as a categorical variable did not significantly decrease the OFV (7.1 points drop for 1df).

In the evaluated studies (VMT-VT-1161-CL-001 to VMT-VT-1161-CL-008), the elevation in total bilirubin was associated with increases in both direct and indirect bilirubin and no subject was diagnosed with underlying liver conditions. In addition, the estimated decrease in CL/F with increased direct (conjugated) bilirubin is challenging to interpret given that the liver is able to conjugate bilirubin and thus oteseconazole, which is a lipophilic molecule primarily eliminated via biliary excretion. In conclusion, the popPK model predicted effect of decreased CL/F with increased total or direct bilirubin levels from the current PK data is likely not clinically relevant and cannot be extrapolated or used to predict oteseconazole exposure under impaired liver function.

Oteseconazole is highly bound to protein (>99%). The Applicant's popPK model found a negative relationship between serum albumin levels and the apparent central volume of distribution, V₂/F. However, all enrolled subjects had normal serum albumin levels. Therefore, the estimated effect of albumin levels on V₂/F, even though statistically significant, is most likely not clinically relevant and cannot be used as a predictor of V₂/F.

Non-Caucasian (not white) subjects were found to have 48% higher CL/F than white subjects, with the majority of non-Caucasian subjects being African American (82%). The backward deletion of race from the Applicant's final popPK model, did not find that race (i.e., Non-Caucasian versus Caucasians) was a statistically significant covariate on CL/F (at a significance level of 0.001), with a change in the OFV by 6 points after removal of the covariate. The covariate plots from the base popPK model did not show any trend in CL/F among the different reported race groups. In addition, the evaluation of the PK of multiple oral doses of oteseconazole in healthy Japanese and Western subjects, from study VMT-VT-1161-CL-003 ([Table 145](#)), did not find a significant difference in C_{max} and AUC(0-72h) between Japanese and Western subjects after accounting for the difference in body weight. Therefore, the estimated effect of race on CL/F, from the Applicant's popPK model, is likely not clinically relevant and could be confounded by unaccounted factors.

The estimated 3-fold higher Ka in study VMT-VT-1161-CL-007, from the Applicant's popPK model, could be due to the fact that the oteseconazole tablet formulation was reportedly administered after a high-fat meal. However, PK evaluation from the different studies did not show differences in the median time to reach maximum oteseconazole concentration after multiple doses either under different formulations, dose levels, fasted/fed conditions, or meal types, with a median T_{max} ranging from 4 to 6 hours after dosing. The covariate plots from the base popPK model could not be used to reliably assess the relationship given the relatively high

ETA shrinkage on K_a . Therefore, the estimated difference in K_a from study VMT-VT-1161-CL-007 is likely not clinically relevant and could be biased by the relatively ETA shrinkage on K_a .

The estimated 47% lower V_2/F in study VMT-VT-1161-CL-002 compared to the other studies is likely due to the higher oteseconazole bioavailability when oteseconazole capsule formulation is administered after a high-fat high-calorie meal. In fact, the noncompartmental PK evaluation from study VMT-VT-1161-CL-001 found that the administration of a single 320-mg dose of oteseconazole capsule with a standard high-fat meal resulted in 3-fold higher C_{max} and a 4-fold higher exposure ($AUC_{0-\infty}$) than those observed in the fasted state in a separate group of subjects. However, in study VMT-VT-1161-CL-013 a moderate effect of food on oteseconazole PK was observed, where the administration of 150 mg oteseconazole (capsule formulation) following a high-fat and high-calorie meal increased mean C_{max} and AUC_{0-72h} by approximately 45% and 36%, respectively, compared with fasting conditions.

The effect of high-fat meal, from study VMT-VT-1161-CL-002, was expected to be reflected on CL/F as well. However, an opposite trend with higher CL/F was observed from the base popPK covariate plots between study VMT-VT-1161-CL-002 and CL/F . Besides, no relationship was observed between diet and CL/F or V_2/F .

This observation could be confounded by the inconsistent extent of food effect between studies, the nonstandardized caloric content of the meals taken prior to dosing between studies, and the estimated 90% lower bioavailability for the over-encapsulated tablets formulation (studies VMT-VT-1161-CL-003 and VMT-VT-1161-CL-004)

Adequacy of the Proposed Fixed Dosing in all Patients (Adolescents to Adults)

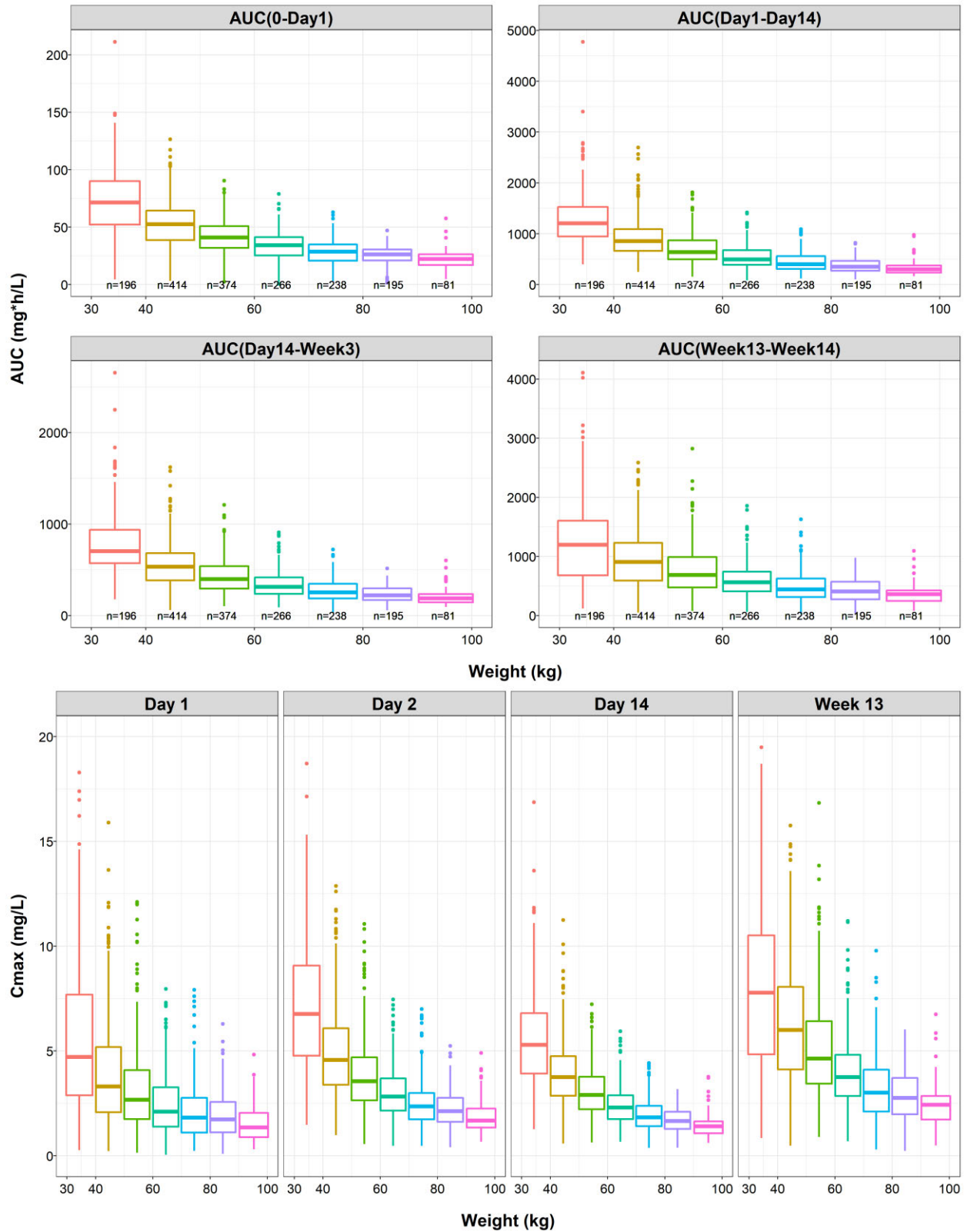
Body weight was a significant covariate in the popPK model. The reviewer conducted simulations using the Applicant's popPK model in adolescent and adult patients, in order to evaluate whether the proposed fixed dosing (regardless of weight) provides comparable exposure of oteseconazole in all patients (adolescents to adults). Monte-Carlo PK simulations were performed to derive exposure parameters (AUC_{τ} , C_{max} , and C_{min}) following the proposed dosing regimen for RVVC (Day 1: 600 mg, Day 2: 450 mg, and Day 14: 150 mg/week for 11 weeks).

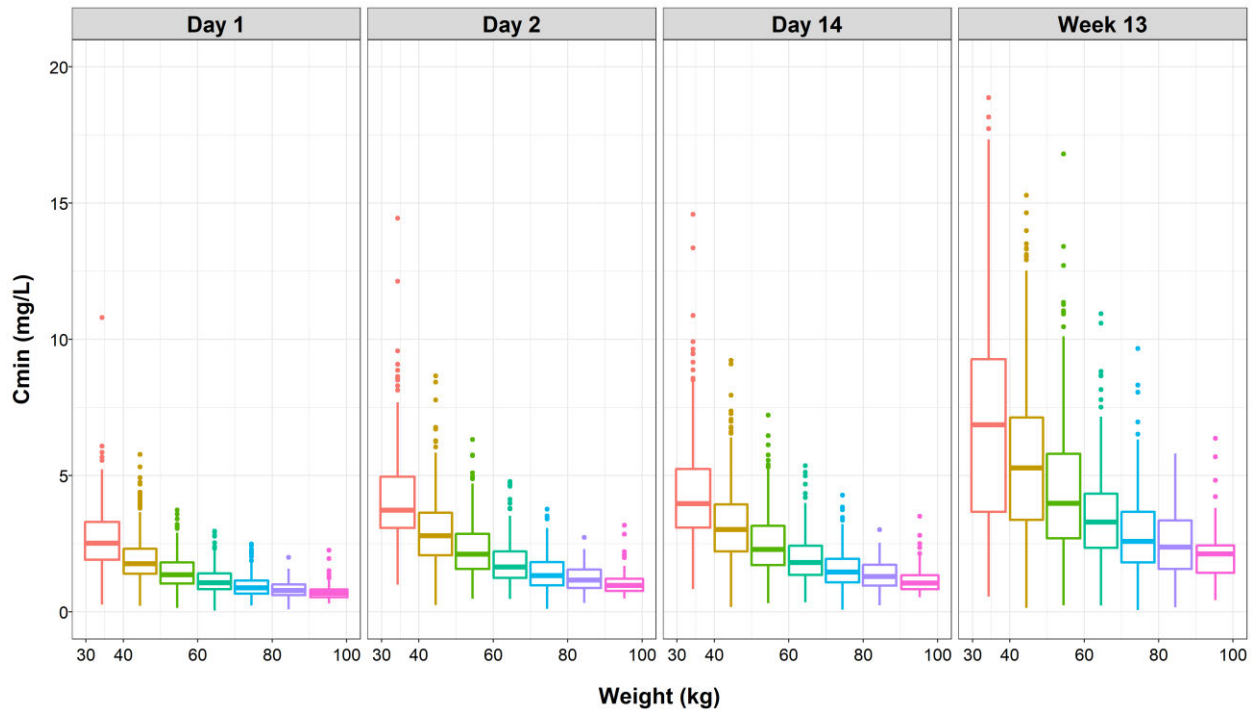
PK simulations were performed using a virtual population ($n=1764$) derived from the Centers for Disease Control and Prevention growth chart (29 to 100 kg). Exposure parameters of oteseconazole for Day 1, Day 2, Day 14, and Week 13 (last maintenance dose) between body weight groups as well as the relative change in exposure metrics from a reference body weight group (60 to 70 kg) are in [Figure 15](#) and [Figure 16](#), respectively.

The PK simulations shows that at lower body weights ranging from 29 to <40 kg (expected to be most prevalent in younger adolescent population < 16 years old), the median AUC_{τ} , median C_{max} , and median C_{min} is about 2-fold the median values observed in patients with body weight ranging from 60 to 70 kg ([Figure 15](#) and [Figure 16](#)).

The clinical studies did not include adolescent patients younger than 16 years old (3 patients with age 16 to 17 years old). No treatment-emergent adverse events (TEAE) were observed in these patients. Only one patient weighing <40 kg was enrolled in the Phase 3 studies (VMT-VT-1161-CL-011, VMT-VT-1161-CL-012, VMT-VT-1161-CL-017), and patients weighing between 40 to 59 kg do not appear to have increased AEs compared to those weighing at least 60 kg. Therefore, given the favorable safety profile of oteseconazole, no dose adjustment based on body weight is warranted in adolescent patients.

Figure 15. Predicted Oteseconazole AUC_T, C_{max}, and C_{min} Under the Proposed Regimen in Adolescent and Adults With Recurrent Vulvovaginal Candidiasis, Stratified by Body Weight.

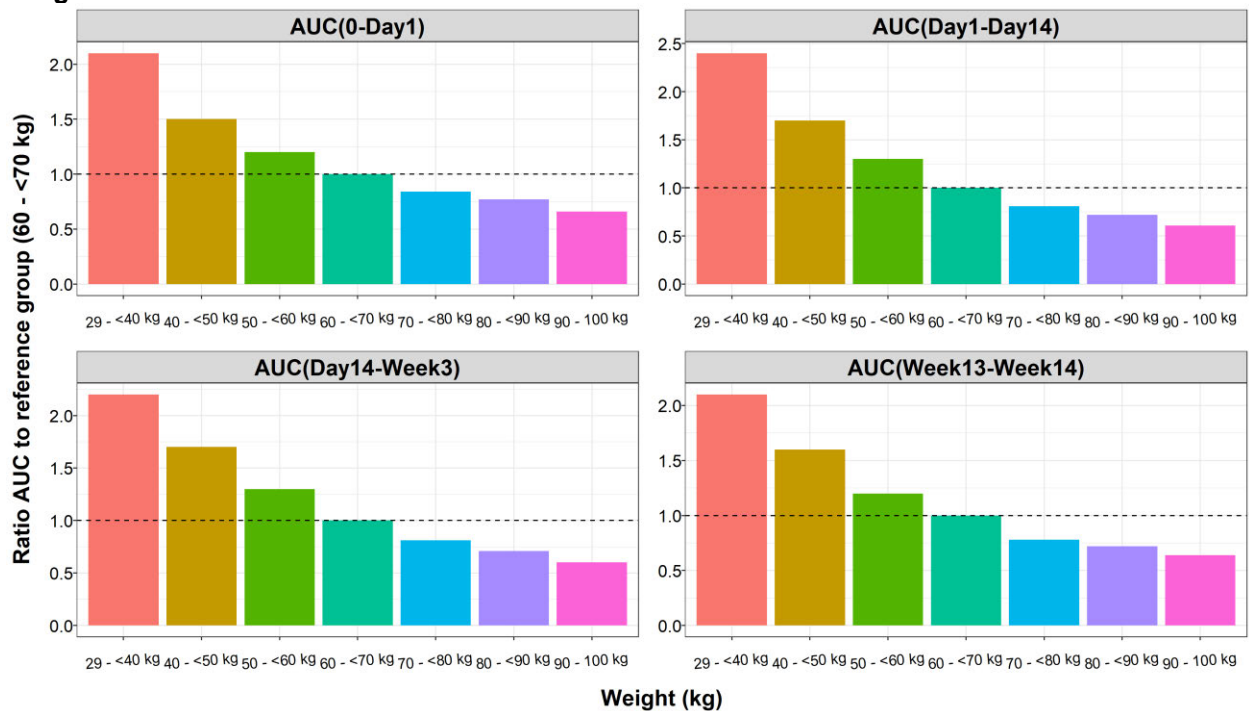


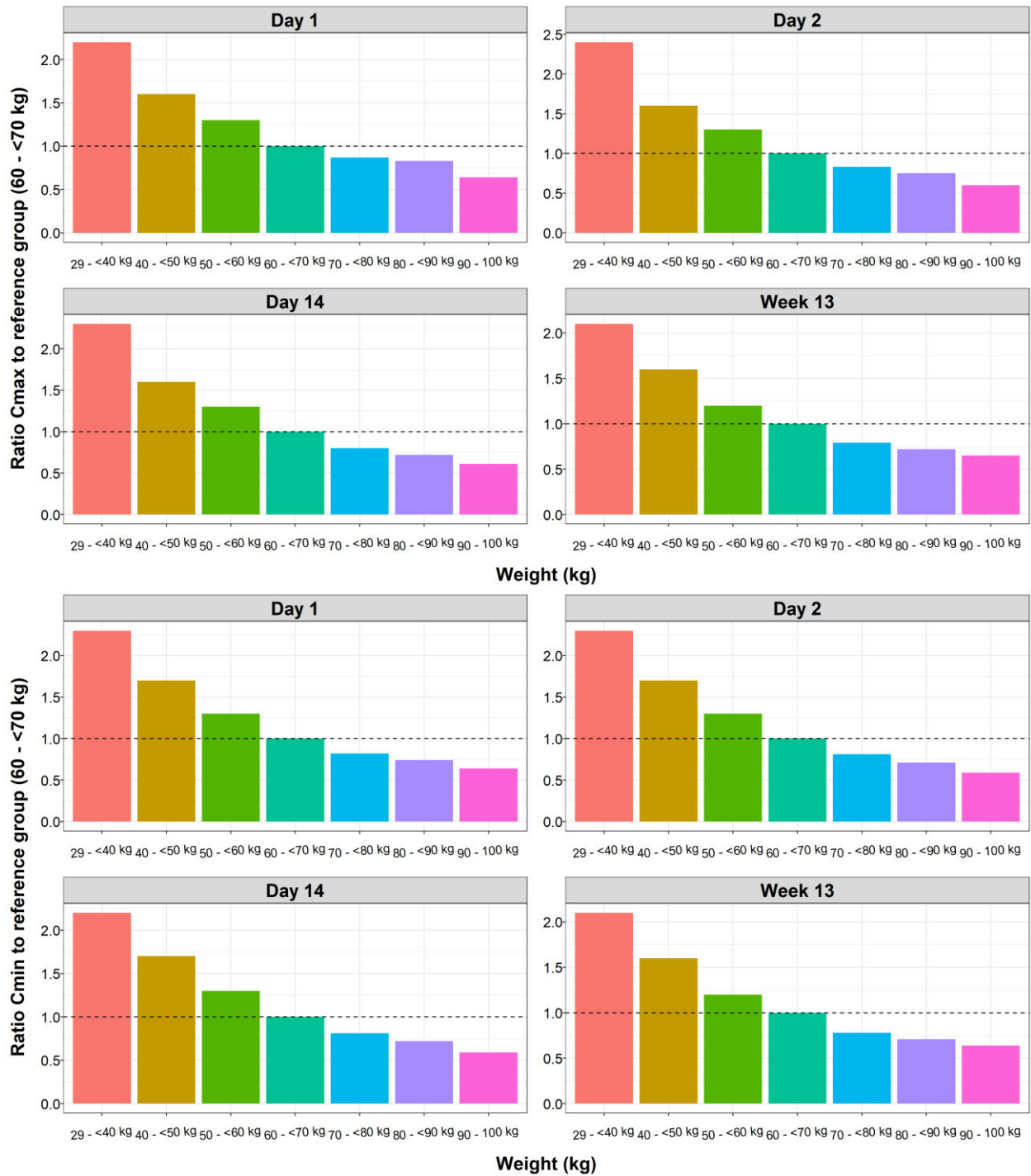


Source: Reviewer's Analysis

Abbreviations: AUC, area under the curve; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration.

Figure 16. Ratio of Median Predicted Oteseconazole AUC_T, C_{max}, and C_{min} Under the Proposed Regimen in Adolescent and Adults With Recurrent Vulvovaginal Candidiasis, Stratified by Body Weight.





Source: Reviewer's Analysis

Note: The vertical dashed line (ratio of 1) represents the ratio in median AUC_τ, C_{max} or C_{min} for the reference group with subject weighing 60 to <70 kg.

Abbreviations: AUC, area under the curve; AUC_{last}, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration.

14.3.3. Appendix

Information Request Addressed to the Applicant on October 4, 2021

The Applicant's population pharmacokinetic analysis identified total bilirubin as covariate on oteseconazole clearance (CL) with an estimated average effect of about 18% lower CL for a total bilirubin level of 1.4 mg/dL, when using the covariate as a time varying continuous variable. The evaluation of elevated total bilirubin as a categorical variable (total bilirubin > 1.2 mg/dL, the upper normal level), using the Applicant PK model, found an average effect of about 26% lower CL for higher total bilirubin levels. Although this relationship was found to be statistically significant, the clinical significance and the physiological explanation of this trend with regard to the elimination pathway of the drug is not clear.

- Please clarify whether subjects with observed high total bilirubin levels were known to have some level of hepatic dysfunction or liver condition resulting in impaired bilirubin conjugation or bilirubin excretion (e.g., cholestasis, Child-Pugh class, etc.).
- Please clarify whether the elevated total bilirubin levels were due to an increase in direct bilirubin or indirect bilirubin.

Evaluate in the popPK model the relation between oteseconazole CL and indirect bilirubin levels, as well as oteseconazole CL and the direct bilirubin levels (as time varying categorical or continuous variables), or any other liver function classification or liver disease. Please provide the population PK analysis dataset with the updated direct and indirect bilirubin levels (keeping the same dataset structure and continuous ID order as the original dataset), as well as the covariate plots for the newly evaluated covariate, and a summary of the updated popPK model parameter estimates in case of any significant new findings in your response to the information request.

14.4. Summary of Bioanalytical Method Validation and Performance

The clinical pharmacology team reviewed the bioanalytical method validation and sample analysis reports for the quantitation of oteseconazole in human plasma, and found the analyses to be acceptable. Validation results for the bioanalytical methods are summarized below.

Table 148. Bioanalytical Methods

	LC/MS/MS
Method Type Validation Report #	VMT11-007
Studies Analyzed	VMT-VT-1161-CL-001, VMT-VT-1161-CL-002, VMT-VT-1161-CL-004, VMT-VT-1161-CL-006, VMT-VT-1161-CL-007 and VMT-VT-1161-CL-008
Biological matrix	Human plasma
Anticoagulant	K ₂ EDTA
Calibration curve	20 – 40,000 ng/mL
Analyte of interest	Oteseconazole
Internal standard	VT-1161- d ₄

Method Type Validation Report #		LC/MS/MS	VMT11-007
Studies Analyzed		VMT-VT-1161-CL-001, VMT-VT-1161-CL-002, VMT-VT-1161-CL-004, VMT-VT-1161-CL-006, VMT-VT-1161-CL-007 and VMT-VT-1161-CL-008	
Method Validation Summary			Acceptability
Intra-run accuracy (for all QC concentrations)		≤5%	Yes
Intra-run precision (for all QC concentrations)		≤7%	Yes
Inter-run accuracy (for all QC concentrations)		-0.4-5.8 (-7.0% LLOQ)	Yes
Inter-run precision (for all QC concentrations)		3.1-7.1 (13.0% LLOQ)	Yes
Selectivity		No interference peaks >20% of LLOQ	Yes
Short-term or bench-top temperature stability		24 hours	Yes
Freeze-thaw stability		4 freeze-thaw cycles at -70°C	Yes
Long-term storage		730 days at -70°C	Yes
Incurring sample reanalysis		CL-001: 90 tested (100% passed) CL-002: 118 tested (100% passed) CL-004: 32 tested (100% passed) CL-006: 79 tested (98.7% passed) CL-007: 115 tested (99.1% passed) CL-008: 127 tested (100% passed)	Yes
Method Type Validation Report #	LC/MS/MS	172014VEA_MDN_R1	
Studies Analyzed	VMT-VT-1161-CL-011, VMT-VT-1161-CL-012, VMT-VT-1161-CL-013, VMT-VT-1161-CL-016 and VMT-VT-1161-CL-017		
Biological Matrix	Human Plasma		
Anticoagulant	K₂EDTA		
Calibration curve	20 – 40,000 ng/mL		
Analyte of interest	Oteseconazole		
Internal standard	VT-1161- d₄		
Method Validation Summary			Acceptability
Intra-run accuracy (for all QC concentrations)		≤5%	Yes
Intra-run precision (for all QC concentrations)		≤7%	Yes
Inter-run accuracy (for all QC concentrations)		-3.0 to 6%	Yes
Inter-run precision (for all QC concentrations)		-2.5 to 6.8%	Yes
Selectivity		No interference peaks >20% of LLOQ	Yes
Short-term or bench-top temperature stability		24 hours	Yes
Freeze-thaw stability		5 freeze-thaw cycles at -70°C	Yes
Long-term storage		781 days at -70°C	Yes
Incurring sample reanalysis		CL-011: 120 ISR samples (94.2% passed) CL-012: 120 ISR samples (99.2% passed) CL016: 45 ISR samples (100% passed) CL-017: 50 ISR samples (98% passed)	Yes

Source: Reviewer's Analysis

Abbreviations: LC/MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control.

NDA 215888
Vivjoa (oteseconazole)

Dilution integrity was verified for each clinical pharmacology study as relevant. The bioanalytical method and sample analysis reports for quantitation of concomitant medications for drug interaction studies were reviewed and found to be acceptable.

15. Trial Design: Additional Information and Assessment

15.1. Trial CL-011 Trial Design Synopsis

A synopsis for Trial VMT-VT-1161-CL-011 (CL-011) from protocol synopsis version 5 (amendment 4) is included in here. Additional details of the multiple imputation methods used for the primary analysis from the statistical analysis plan are described following the synopsis. Trial VMT-VT-1161-CL-012 (CL-012) had an identical design as CL-011.

APPEARS THIS WAY ON ORIGINAL

PROTOCOL SYNOPSIS

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis
Protocol Number: VMT-VT-1161-CL-011
Interim Analysis: No
Investigational Medicinal Product: VT-1161 capsules
Non-Investigational Medicinal Product: Fluconazole tablets or capsules
Planned Number of Sites: 60 to 80
Planned Number of Subjects: 600 screened; 300 randomized
Phase of Development: 3
Introduction: VT-1161 is an orally-available inhibitor of fungal CYP51 that has shown high potency and selectivity in <i>in vitro</i> studies. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane, which is critical to fungal growth. <i>In vitro</i> and <i>in vivo</i> pharmacology studies have demonstrated that VT-1161 is highly active against <i>Candida albicans</i>, including fluconazole-resistant <i>C. albicans</i>, and non-<i>albicans Candida</i> species that cause vulvovaginal candidiasis (VVC). VT-1161 is highly selective for fungal CYP51 relative to off-target human CYP enzymes, and data to date suggest that it may avoid the side-effect profile that limits the use of commonly prescribed azole antifungal agents. Oral VT-1161 has been evaluated in Phase 1 and 2 studies and shown to be safe, well tolerated, and highly effective in the treatment of vulvovaginal infections caused by <i>Candida</i> species. For example, in a Phase 2b study in subjects with recurrent VVC (RVVC), subjects in the 12-week VT-1161 treatment group (150 mg VT-1161 once daily for 7 days followed by 150 mg VT-1161 once weekly for 11 weeks) showed a 4.8% recurrence rate through Week 48 compared with a 52% recurrence rate in the placebo group in the intent-to-treat analysis. RVVC, defined as 3 or more acute VVC episodes over a 12-month period, is experienced by 5 to 7 million women each year in the US. <i>Candida albicans</i> is the leading cause of recurrent vulvovaginal yeast infections in the United States. However, there has been an increasing trend in the number of vaginal yeast infections attributable to non-<i>albicans</i> species such as <i>C. glabrata</i> and <i>C. tropicalis</i>. In addition to the use of topical products to treat VVC, the majority of the women visiting healthcare professionals receive fluconazole for the treatment of each acute episode. A smaller percentage are prescribed a fluconazole maintenance regimen although fluconazole is not currently approved for the treatment of RVVC. Since some of the <i>C. albicans</i> and the majority of non-<i>albicans</i> isolates are resistant to fluconazole, the management of RVVC has become even more challenging. In both nonclinical studies and clinical trials conducted to date, VT-1161 has demonstrated a favorable safety and tolerability profile, with no discernable adverse effect on liver function. In reproductive toxicity studies in pregnant rats or rabbits, VT-1161 was not teratogenic at any exposure studied. In a recent CYP3A4 drug-drug interaction study utilizing midazolam as the substrate, no clinically significant inhibition and only weak induction of midazolam metabolism was observed. These data are favorable when compared to other oral antifungal agents such as fluconazole.

Objectives:

Primary:

- To evaluate the efficacy of oral VT-1161 in the treatment of RVVC through Week 48.

Secondary:

- To evaluate the safety and tolerability of oral VT-1161 in the treatment of RVVC through Week 48.
- To evaluate the impact of oral VT-1161 treatment on patient reported outcomes through Week 48.

Methodology:

Study Design:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study will evaluate the efficacy and safety of oral VT-1161 capsules in the treatment of subjects with RVVC. The impact of oral VT-1161 treatment will also be evaluated using data collected from patient reported outcome assessments.

Subjects must have a history of RVVC, defined as at least 3 episodes of acute VVC in the past 12 months, as described below:

- Subjects must have an acute VVC episode at the time of Screening, with a documented positive potassium hydroxide (KOH) or Gram stain performed at the investigative site
- Subjects must also have had 2 or more additional episodes of acute VVC in the past 12 months, with at least 1 of the episodes documented by a positive confirmatory laboratory test (i.e., culture, PCR, Affirm test, KOH test, Gram stain, a documented Papanicolaou (Pap) test, or other approved diagnostic tests)

The study consists of two Phases: 1) an open-label Induction Phase for the treatment of the acute VVC episode with 3 sequential 150 mg oral doses (every 72 hours) of fluconazole, and 2) a Maintenance Phase in which subjects will be randomly assigned to receive VT-1161 or placebo for 7 daily doses followed by 11 weekly doses and will then enter a 36-week follow-up period.

Once subjects have provided informed consent or assent (for those ages 12 to 17), the investigational site will evaluate all subjects by completing a review of pertinent medical history, obtaining vital signs, weight and height, electrocardiogram (ECG) and laboratory tests, reviewing clinical signs and symptoms of vulvovaginitis, performing a complete physical examination including speculum examination of the vagina, performing a KOH wet mount test or Gram stain from a vaginal smear to confirm the presence of yeast, and collecting vaginal swabs to establish a baseline culture for identification of fungal species. Patient reported outcome surveys (SF-36, EQ-5D-3L or EQ-5D-Y (for ages 12 to 17), WPAI:SHP, PHQ-9) for all regions and questions regarding their RVVC history (US only) will also be administered. Eligible subjects must have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥ 3 and a positive local KOH wet mount preparation or Gram stain from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells, and must meet other initial entry criteria. Once eligibility is confirmed, subjects will enter the Induction Phase. During the Induction Phase, the presenting acute VVC infection will be treated with 3 sequential 150 mg oral doses (every 72 hours) of fluconazole. Subjects will return approximately 14 days after the first dose of fluconazole

for evaluation. If the clinical signs and symptoms of the acute VVC infection have resolved (defined by a signs and symptoms score of <3), they will be randomized in a 2:1 ratio to receive either VT-1161 or a matching placebo regimen. Day 1 (Baseline) is defined as the first day of investigational medicinal product (IMP) administration and subsequent study days are defined by the number of consecutive days thereafter. If the acute VVC has not resolved (defined by a signs and symptoms score of ≥ 3), the subject will be considered a screen failure and encouraged to see their physician for follow-up care.

Study Duration:

The planned study duration is expected to be approximately 26 months from screening of the first subject until last follow-up of the last subject.

Subject Participation:

The duration of individual subject participation will be approximately 50 weeks, including the 2-week Induction Phase. See [Table 1 for the Schedule of Assessments and Procedures](#) which will be performed. After Screening, subjects will return to the clinic on Day 1 (Baseline), the start of the Maintenance Phase. Subjects will then have visits on Day 14 (± 2 days), Weeks 6 (± 7 days), 12 (± 14 days), 18 (± 14 days), 24 (± 14 days), 30 (± 14 days), 36 (± 14 days), 42 (± 14 days) and 48 (± 14 days) (end of study [EOS]). Subjects who return to the clinic with a recurrent acute VVC episode should be evaluated as per the unscheduled visit noted in the Schedule of Assessment and Procedures.

Scoring of Vulvovaginal Signs and Symptoms:

Vulvovaginal signs and symptoms will be evaluated at Screening and at each subsequent study visit. Each of the following vulvovaginal signs and symptoms will be scored and the individual scores combined, for a maximum score of 18 using the following scale:

- a. Signs: erythema, edema, and excoriation
- b. Symptoms: itching, burning, and irritation

Scoring Scale: Each score should be graded on a scale of 0 to 3 as follows:

- 0 = none (complete absence of any sign or symptom)
- 1 = mild (slight)
- 2 = moderate (present)
- 3 = severe (marked, intense)

Mycology Assessment:

A local mycological assessment using KOH wet mount followed by microscopy or Gram stain will be evaluated at the Screening and at any study visit where a recurrent acute VVC episode is suspected. The investigative site is to use the same local mycology test (KOH or Gram stain) consistently for all subjects throughout the study. In addition, a vaginal swab for culture testing will be obtained and sent to the central mycology laboratory at the Screening and each subsequent study visit.

Plasma Pharmacokinetics:

Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects at Baseline, Day 14, and Weeks 12, 24, 36, 48 and unscheduled visits.

<u>Safety:</u> Subject safety will be monitored by collection of adverse events (AEs), changes in vital signs, physical and vaginal exam parameters, ECGs, and safety laboratory parameters, including pregnancy tests for women of childbearing potential (WOCBP).
Concomitant Medications: The following prescription and over-the-counter drug products are prohibited during the study and will be considered a protocol deviation: 1. Topical or oral antifungal drugs (with the exception of fluconazole when prescribed by the Investigator to treat a subject with a recurrent VVC episode; refer to Section 8.1.12 on treatment options if fluconazole is ineffective). 2. Topical products applied to the vulva or vagina (e.g. antibiotic, antitrichomonal, corticosteroids, or anti-inflammatory agents). 3. Oral antibacterial or antitrichomonal agents for the treatment of bacterial vaginosis, trichomonas, or other concomitant (urogenital) infection unless prescribed by the Investigator. 4. Oral or injectable corticosteroid or immunosuppressive drugs for the duration of the study. Use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, collunarium/nasal, or intraarticular and intralesional steroids is permitted. 5. Drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus). 6. Vaginal douches or benzalkonium chloride disinfectant during the study.
Number of Subjects (Planned): Approximately 600 screened and 300 randomized subjects are planned for this study. Assuming a 20% discontinuation rate for the duration of the study, approximately 240 subjects are expected to complete the study.
Criteria for Inclusion and Exclusion: <u>Criteria for Inclusion:</u> 1) Subjects must be generally healthy, post-menarchal, non-pregnant females 12 years of age and older as of Screening. 2) Subjects must have a history of recurrent VVC as defined by three (3) or more episodes of acute VVC in the past 12 months, including the episode confirmed at Screening, with at least one episode (not including the current episode) documented by a positive culture, PCR, Affirm test, KOH test, Gram stain or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells, or other approved diagnostic tests. 3) Subjects must have an acute VVC episode at Screening, defined as: a. a total signs and symptoms score of ≥ 3 and b. a positive KOH wet mount preparation or Gram stain from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells. 4) Subjects must have a composite vulvovaginal signs and symptoms score of < 3 at the Baseline (Day 1) Visit. 5) Subjects must have a documented Pap test at Screening or within the timeline per current standard of care guidelines for the appropriate age requirement. Results must be either "negative for

- intraepithelial lesion or malignancy” or “ASCUS-atypical squamous cells of undetermined significance” (not applicable to subjects with a history of total hysterectomy).
- 6) Subjects must be suitable candidates for oral therapy and be able to swallow capsules intact.
 - 7) Subjects must be willing and able to provide written informed consent or assent (for those ages 12 to 17) and authorization for use of protected health information.
 - 8) Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned.
 - 9) Subjects of non-childbearing potential must meet the requirements defined below:
 - a. Pre-menopausal with documentation of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) at least 3 months prior to Screening.
 - b. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments at Screening.
 - 10) Subjects of childbearing potential (includes ages 12-17) must use 1 of the following methods of contraception during the study through Week 48:

OPTION 1 – Highly effective methods that can be used alone:

- i. Copper intrauterine device
- ii. Levonorgestrel-releasing intrauterine system
- iii. Progestin implant
- iv. Monogamous with a vasectomized male partner
- v. Abstinence^a

OPTION 2 – Acceptable first and second barrier methods to be used in combination:

FIRST (Hormonal Contraception)^b

1. Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring.
2. Progestin only oral contraceptives or injection

SECOND (Barrier Method)

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)
3. Male condom (with or without spermicide)

In addition to OPTIONS 1 and 2, subjects of childbearing potential (includes ages 12-17) may also use 1 of the following methods of contraception after completing the Induction Phase on Study Day 1 through Week 48:

OPTION 3 (Day 1 – Week 48)^c – Acceptable first and second barrier methods to be used in combination:

FIRST (Barrier Method)

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)

SECOND (Barrier Method)

1. Male condom (with or without spermicide)

^a Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and where this is the usual life style of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception.

^b Subjects who started taking a hormonal contraceptive less than 3 months prior to the first dose of

fluconazole must agree to use a double-barrier method (i.e. diaphragm plus spermicide or condom) through 3 months after starting the hormonal contraceptive.

*Because of the teratogenic risk associated with repeat dosing of fluconazole, OPTION 3 contraceptive methods cannot be used during Screening and the Induction Phase of the study [from Screening until Baseline (Day 1) of the study].

Criteria for Exclusion:

- 1) Subjects must not have the presence of concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*) at Screening visit and at the Day 1 visit if an infection is suspected.
- 2) Subjects must not have an active HPV infection as evidenced by visible condylomas on vulvovaginal examination at Screening and Day 1 visits.
- 3) Subjects must not have the presence or a history of another vaginal or vulvar condition(s) that in the Investigator's opinion would confound the interpretation of clinical response.
- 4) Subjects must not have a history of cervical cancer.
- 5) Subjects must not use any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to Screening, nor use of topical vulvar or vaginal steroids during the study or within 7 days prior to Screening. However, use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, collunarium/nasal, intraarticular and intralesional steroids is permitted.
- 6) Subjects must not use any systemic (e.g., oral or injectable) or topical (applied to the vulva or vaginal area) antifungal, antibacterial, or antitrichomonal drugs or vaginal douches during the study (unless prescribed by the Investigator) or within 7 days prior to Screening.
- 7) Subjects must not be using drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 during the study (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).
- 8) Subjects must not use any vaginal estrogen replacement therapy, ospemifene, Vitamin E gel capsules (vaginally) or lubricants within 7 days prior to Screening.
- 9) Subjects must not have a condition that would require treatment during the study with concomitant topical (applied to vulva and vagina) or systemic antimicrobial therapy for any reason.
- 10) Subjects must not have received an immunosuppressive medication (e.g. cyclosporine, tacrolimus, methotrexate, 6-mercaptopurine, mycophenolate, etc.), or radiation therapy within 3 months prior to Screening or have a medical condition where it would be likely that the subject may need to use these therapies during the study.
- 11) Subjects must not have evidence of any clinically significant major organ disease or current clinically significant infection or any other conditions (with the exception of acute VVC) that may affect the clinical assessment of RVVC per investigator judgment.
- 12) Subjects must not have any comorbid condition that in the opinion of the Investigator would preclude the safe participation of the subject in the study or would prevent the subject from meeting the study requirements.
- 13) Subjects must not have any condition that in the opinion of the investigator could impact drug absorption (e.g. gastrectomy, Roux-en-Y gastric bypass surgery, gastric bands or staples, etc.), distribution, or elimination.
- 14) Subjects must not have poorly controlled diabetes mellitus (HbA1c $\geq$ 8.5% at Screening).
- 15) Subjects must not have moderate or severe hepatic and/or renal disease (defined in [Appendix B](#) and [Appendix C](#)).

- 16) Subjects must not have a laboratory abnormality that in the opinion of the Investigator is likely to introduce additional risk to the subject or might interfere with data interpretation. The specific findings listed below are excluded at Screening (a single repeat laboratory evaluation is allowed for eligibility determination, except for HIV, HbsAg and antibodies to hepatitis C virus):
- a. Serum alanine aminotransferase (ALT) ≥ 2.0 x the upper limit of normal (ULN) of the reference range.
 - b. Serum aspartate aminotransferase (AST) ≥ 2.0 x the ULN of the reference range.
 - c. Serum total bilirubin ≥ 1.5 x the ULN of the reference range, unless the elevation is consistent with Gilbert's Syndrome.
 - d. Electrocardiographic QTc interval >470 msec as corrected by the Fridericia formula, or any clinically significant electrocardiographic abnormality.
 - e. Positive test for antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or antibodies to hepatitis C virus.
- 17) Subjects of childbearing potential must not be pregnant (positive pregnancy test at Screening), lactating, or planning to become pregnant during the study period.
- 18) Subjects must not have planned surgery or other medical procedures that in the Investigator's opinion would impact compliance with the protocol.
- 19) Subjects must not have active substance abuse (e.g., drugs of any kind, including alcohol) or any other medical, psychiatric or social condition that in the Investigator's opinion would preclude compliance with the protocol.
- 20) Subjects must not have received VT-1161 study medication in a previous study.
- 21) Subjects must not have received any IMP in a clinical trial within 5 half-lives of that IMP prior to Screening (if unknown, 60 days prior to Screening).
- 22) Subjects must not have a known history of intolerance or hypersensitivity to azole antifungal drugs (e.g., fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole), or any excipients of the capsule formulation.

Induction Phase Treatment: Fluconazole 150 mg tablets or capsules

Dose and Mode of Administration:

Oral administration of 3 sequential doses (every 72 hours) of fluconazole 150 mg starting at Screening (Day -14).

Maintenance Phase Test Product: VT-1161 150 mg capsules

Dose and Mode of Administration:

Oral administration of VT-1161 within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Starting at Baseline (Day 1), loading doses of 150 mg (1 capsule) once daily for 7 days, followed by doses of 150 mg (1 capsule) once weekly for 11 weeks.

Duration of Administration: 12 weeks

Maintenance Phase Reference Product: Matching Placebo capsules <u>Dose and Mode of Administration:</u> Oral administration of placebo within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP. Starting at Baseline (Day 1), loading doses of placebo once daily for 7 days, followed by doses of placebo (1 capsule) once weekly for 11 weeks. <u>Duration of Administration:</u> 12 weeks
Study Populations: <u>Intent-to-Treat (ITT) Population:</u> All randomized subjects. <u>Safety Population:</u> All randomized subjects who received at least 1 dose of IMP. <u>Per Protocol Population (PP):</u> All randomized subjects who had the following: • Had no deviations to inclusion/exclusion criteria that could impact treatment outcome. • Were compliant with the assigned study treatment, defined as $\geq 80\%$ compliance during the daily dosing phase and $\geq 50\%$ compliance during the weekly dosing phase. • Had the Week 48 visit completed within the acceptable time window (± 14 days). • Had no major protocol violations that would impact treatment outcome. <u>Modified ITT:</u> All randomized subjects who had the following: • Positive KOH or Gram stain at Screening. • Positive culture at Screening. • Negative culture at Baseline.
Criteria for Evaluation: <u>Efficacy:</u> Clinical and mycological assessments will be conducted as outlined in Table 1. Schedule of Assessments and Procedures. All efficacy analyses will be performed on the ITT, PP, and mITT Populations. The primary efficacy outcome measure is the proportion of subjects with one or more culture-verified acute VVC episodes during the Maintenance Phase (post-randomization through Week 48) in the ITT population. An acute VVC episode during the Maintenance Phase (considered a recurrent episode) is defined as a positive culture for <i>Candida</i> species and a clinical signs and symptoms score of ≥ 3. The key secondary efficacy outcome measures include the following: a. Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥ 3 during the Maintenance Phase. b. The proportion of subjects with at least one positive culture for <i>Candida</i> during the Maintenance Phase.

- c. The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms of ≥ 3 post randomization through Week 24.
- d. Change from Screening through Week 48 in the SF-36 mental component score (MCS).
- e. Change from Screening through Week 48 in the SF-36 patient reported outcome survey total score.

Safety:

All safety analyses will be performed on the Safety Population. AEs will be collected throughout the study. Physical and vaginal examination findings and vital signs will be recorded at Screening and throughout the study per Table 1. [Schedule of Assessments and Procedures.](#)

ECGs and safety laboratory tests (hematology, chemistry, and urinalysis) will be obtained throughout the study. All concomitant medications taken during the period from 30 days prior to Screening through the Week 48 (EOS) visit will be recorded in the case report form (CRF). Pertinent and all major medical conditions will be recorded on the Medical History CRF.

Subject who want to discontinue from the study should be encouraged to remain in the study for all remaining visits through Week 48 for safety and efficacy assessments. All subjects who discontinue early from the study should have all EOS procedures performed on the day of discontinuation.

Statistical Methods and Data Analysis:

A statistical analysis plan will be finalized before 50% of subjects are enrolled.

Efficacy Analysis:

The primary statistical objective of this study is to determine if there are differences in the proportions of subjects with one or more episodes of culture-verified acute VVC in those receiving VT-1161 compared to those receiving placebo during the Maintenance Phase.

A sample size of 68 active subjects and 34 placebo subjects provides at least 95% power to detect a treatment difference of 35% between the VT-1161 treatment group and the placebo treatment group in percentage of subjects with at least one or more culture-verified acute VVC episodes during the Maintenance Phase (post randomization through Week 48). (PASS 2008: Fisher's exact test, two-sided $\alpha=0.05$, and assuming 50% of placebo subjects have recurrence). Based on an estimated 20 % discontinuation rate, approximately 128 total subjects (85 active, 43 placebo) will be necessary for randomization to arrive at approximately 102 evaluable subjects.

Safety Analysis:

AEs will be coded using the Medical Dictionary for Regulatory Activities® dictionary. The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by system organ class, preferred term, and greatest severity with a breakdown by treatment group. Mean changes from pre-treatment in vital signs, ECG, and clinical laboratory variables will be summarized by treatment group.

Pharmacokinetics:

No formal statistical hypothesis testing related to pharmacokinetics will be conducted. VT-1161 concentrations will be presented by visit with descriptive statistics. The pharmacokinetic data will be

used in a cross-population pharmacokinetic analysis that will be presented in a separate report.

Patient Reported Outcomes:

The SF-36, EQ-5D-3L or EQ-5D-Y (for ages 12 to 17), WPAI-SHP, and PHQ-9 patient reported outcome surveys will be administered at Screening, Week 24 (EOT) and Week 48 (EOS) for all regions. At Screening, subjects will also be required to answer questions regarding their RVVC history (US only).

Table 1. Schedule of Assessments and Procedures

Activities	Screening Day -14, (±2 days)	Baseline (Day 1)	Day 14 (±2 days)	Week 6 (±7 days)	Week 12 (±14 days) EOT	Week 18 (±14 days)	Week 24 (± 14 days)	Week 30 (± 14 days)	Week 36 (± 14 days)	Week 42 (± 14 days)	Week 48 (± 14 days) EOS	Unscheduled Visit ⁱ
Sign Informed Consent or Assent Form	X											
Inclusion/Exclusion Criteria	X	X										
Medical/Surgical History	X											
Prior/Concomitant Medications/Treatments ^a	X	X	X	X	X	X	X	X	X	X	X	X
Collect and Record AEs		X	X	X	X	X	X	X	X	X	X	X
Patient Reported Outcome Surveys ^b	X						X				X	X
RVVC History Questionnaire (US Only)	X											
Body Height and Weight	X				X ^c		X ^c				X ^c	
Vital Signs ^d	X	X	X	X	X	X	X	X	X	X	X	X
Physical and Vaginal Examination	X	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e
Clinical Signs and Symptoms of Vulvovaginitis	X	X	X	X	X	X	X	X	X	X	X	X
Local KOH Wet Mount or Gram Stain	X											X
Central Vaginal Fungal Culture	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X		X		X				X	
PK Samples ^f		X	X		X		X		X		X	X
Clinical Laboratory Samples ^g	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X		X		X		X	
Hematology (CBC with differential)	X	X	X		X		X		X		X	
HIV Ab, HbsAg, anti-HCV	X											
Central Serum Pregnancy Test ^h (WOCBP)	X	X			X		X				X	
Local Urine Pregnancy Test ^h (WOCBP)	X	X	X	X	X	X	X	X	X	X	X	X
Administer Fluconazole	X											
Randomization		X										
Administer and/or Review IMP ⁱ		X	X	X	X							

Abbreviations noted above – AEs: adverse events; CBC, complete blood count; ECG: electrocardiogram; EOS: End of Study; EOT: End of Treatment; HbsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; IMP, investigational medicinal product; KOH: potassium hydroxide prep; PK: pharmacokinetic; WOCBP: women of childbearing potential.

- All medication taken 30 days prior to Screening and all non-pharmacologic treatments received 72 hours prior to Screening will be recorded through the EOS visit.
- SF-36, EQ-5D-3L or EQ-5D-Y (for ages 12 to 17), WPAI:SHIP, and PHQ-9 patient reported outcome surveys.
- Weight only.
- Vital signs include sitting heart rate, blood pressure, temperature, and respiratory rate.
- Limited physical examination, i.e. vaginal speculum examination plus a symptom directed physical examination.
- PK Samples should be collected before the weekly dosing of study drug (placebo/VT-1161).
- Serum chemistry (creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, conjugated bilirubin, albumin, total protein, total carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus, creatine phosphokinase [CK], cholesterol, and triglycerides). Testing for HbA1c is performed at Screening. Cultures to test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* will be taken at Screening and sent to the central lab. Testing for bacterial vaginosis will be done locally at Screening. An OSOM[®] Rapid test or similar test will be performed for *Trichomonas vaginalis* locally at Screening.
- For WOCBP, a local lab urine pregnancy test will be performed at every study visit. A central lab serum pregnancy test will also be performed at Screening, Baseline, and Weeks 12, 24, and 48.
- IMP is to be administered within 30 minutes after the subject's main meal of the day (as determined by the subject) at approximately the same time of the day consistently throughout the study. Approximately 240 mL (approx. 8 oz.) of water is to be consumed with each dose of IMP. Remind subject to bring IMP to each visit to ensure compliance.
- All procedures listed are to be completed only for unscheduled visits where a recurrent VVC episode is suspected. If the unscheduled visit is for repeat procedures (i.e., ECG, safety labs, etc.), only those specific procedures need to be performed, along with collection of any changes in medical treatments or medications and collection of any AEs.

- intraepithelial lesion or malignancy” or “ASCUS-atypical squamous cells of undetermined significance” (not applicable to subjects with a history of total hysterectomy).
- 6) Subjects must be suitable candidates for oral therapy and be able to swallow capsules intact.
 - 7) Subjects must be willing and able to provide written informed consent or assent (for those ages 12 to 17) and authorization for use of protected health information.
 - 8) Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned.
 - 9) Subjects of non-childbearing potential must meet the requirements defined below:
 - a. Pre-menopausal with documentation of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) at least 3 months prior to Screening.
 - b. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments at Screening.
 - 10) Subjects of childbearing potential (includes ages 12-17) must use 1 of the following methods of contraception during the study through Week 48:
 - OPTION 1 – Highly effective methods that can be used alone:**
 - i. Copper intrauterine device
 - ii. Levonorgestrel-releasing intrauterine system
 - iii. Progestin implant
 - iv. Monogamous with a vasectomized male partner
 - v. Abstinence^a
 - OPTION 2 – Acceptable first and second barrier methods to be used in combination:**
 - FIRST (Hormonal Contraception)^b**
 1. Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring.
 2. Progestin only oral contraceptives or injection
 - SECOND (Barrier Method)**
 1. Diaphragm (with spermicide)
 2. Cervical cap (with spermicide)
 3. Male condom (with or without spermicide)
- In addition to OPTIONS 1 and 2, subjects of childbearing potential (includes ages 12-17) may also use 1 of the following methods of contraception after completing the Induction Phase on Study Day 1 through Week 48:
- OPTION 3 (Day 1 – Week 48)^c – Acceptable first and second barrier methods to be used in combination:**
 - FIRST (Barrier Method)**
 1. Diaphragm (with spermicide)
 2. Cervical cap (with spermicide)
 - SECOND (Barrier Method)**
 1. Male condom (with or without spermicide)
- ^a Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and where this is the usual life style of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception.
- ^b Subjects who started taking a hormonal contraceptive less than 3 months prior to the first dose of

Additional Information

The following is from Section 3.4.4 and 3.4.8 of the Statistical Analysis Plan for Trial CL-011 (dated 7/25/2020)

3.4.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized, including those who discontinue the study prior to the end-of-study Week 48 visit.

For scheduled visits where the investigator's assessment of clinical signs and symptoms or the culture result is missing, missing values will be imputed using the method of multiple imputation. For subjects who discontinue the study early and have missing assessments for all visits after discontinuation, the missing values for the expected scheduled visits will be imputed using the method of multiple imputation. The missing values will be imputed using the following auxiliary information: region, treatment, baseline BMI, baseline age, ethnicity, and visit. Region, treatment, baseline BMI, baseline age, ethnicity, and visit are included as auxiliary information because it is believed that subjects with similar values for each of these parameters would respond similarly. One of the benefits of using multiple imputation is that it uses a set of values rather than a single value which better accounts for the uncertainty about the values being imputed. The procedure PROC MI in SAS will be used to generate 10 possible imputed datasets. Using these multiple imputation datasets, determination of meeting the primary endpoint of a culture-verified acute VVC episode during the Maintenance Phase will be derived. Subjects with a culture-verified acute VVC episode at any point from post randomization through Week 48 (including unscheduled visits) will be counted as having an episode when calculating the primary endpoint. The multiple datasets containing the primary endpoint will be analyzed using a Chi-square test and the results will be combined using PROC MIANALYZE to obtain an inferential result. Here is a summary of the steps that will be performed:

- (1) For subjects with a missing value for clinical signs and symptoms or a missing value for culture result at a scheduled visit, who have an unscheduled visit (within the visit window) with non-missing values as outlined in Section 3.4.8 [described below], their values from the unscheduled visit will be used to replace scheduled visit values.
- (2) Any missing values for clinical signs and symptoms or culture result for scheduled visits will be imputed using PROC MI. Any unscheduled visit values that are not used to replace scheduled visit values, as described in Step 1, will not be used in the imputation process. The seed for the imputation procedure will be randomly generated and documented in the study files. This will result in 10 complete datasets.
- (3) The primary efficacy endpoint of culture-verified acute VVC episode will be derived using values from all scheduled visits from the complete datasets and all unscheduled visits that were not already used in Step 1. In other words, if an unscheduled visit for a subject is already being used to replace a missing visit in Step 1, then it would not be used again as an unscheduled visit when calculating the primary endpoint. This will result in 10 datasets with one record per person for the primary endpoint.
- (4) The primary efficacy endpoint will be analyzed 10 times using a Chi-square test as outlined in Section 5.2.1. The Wilson-Hilferty transformation will be applied to the Chi-square test statistics prior to combining the results using PROC MIANALYZE.
- (5) The results from the analysis from the 10 datasets will be combined using PROC MIANALYZE to produce an inferential result comparing the treatment groups.

3.4.8. Visit Windows

The visits will be used as nominally recorded in the electronic data collection system. Unscheduled visits will be windowed based on the Study Day at which they occur but will only be used if the scheduled visit is not available. The exception to this will be for the primary and key secondary endpoints where an unscheduled visit with a culture-verified acute VVC episode with signs and symptoms of ≥ 3 will result in the subject being considered as a failure. Unscheduled visits will be windowed based on [Table 149](#) below.

Table 149. Visit Windows for Early Termination and Unscheduled Visits

Nominal Visit	Visit Window
Day 1	Study Day ≤ 1
Day 14	Study Day 12 to 16
Week 6	Study Day 35 to 49
Week 12	Study Day 70 to 98
Week 18	Study Day 112 to 140
Week 24	Study Day 154 to 182
Week 30	Study Day 196 to 224
Week 36	Study Day 238 to 266
Week 42	Study Day 280 to 308
Week 48	Study Day 322 to 350

Source: Table 1 of Statistical Analysis Plan dated July 25, 2020 for Trial CL-011

15.2. Trial CL-017 Trial Design Synopsis

A synopsis for Trial VMT-VT-1161-CL-017 (CL-017) adapted from protocol synopsis version 2 (dated January 17, 2019).

APPEARS THIS WAY ON ORIGINAL

PROTOCOL SYNOPSIS

Title of Study: A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules versus Fluconazole and Placebo in the Treatment of Acute Vulvovaginal Candidiasis Episodes in Subjects with Recurrent Vulvovaginal Candidiasis
Protocol Number: VMT-VT-1161-CL-017
Interim Analysis: No
Investigational Medicinal Product: VT-1161 capsules
Non-Investigational Medicinal Product: Fluconazole tablets
Planned Number of Sites: Approximately 45 U.S.
Planned Number of Subjects: 360 screened; 180 randomized
Phase of Development: 3
Introduction: VT-1161 is an orally-available inhibitor of fungal CYP51 that has shown high potency and selectivity in <i>in vitro</i> studies. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane, which is critical to fungal growth. <i>In vitro</i> and <i>in vivo</i> pharmacology studies have demonstrated that VT-1161 is highly active against <i>Candida albicans</i> , including fluconazole-resistant <i>C. albicans</i> , and non-albicans <i>Candida</i> species that cause vulvovaginal candidiasis (VVC). VT-1161 is highly selective for fungal CYP51 relative to off-target human CYP enzymes, and data to date suggest that it may avoid the side-effect profile that limits the use of commonly prescribed azole antifungal agents. Oral VT-1161 has been evaluated in Phase 1 and 2 studies and shown to be safe, well tolerated, and highly effective in the treatment of vulvovaginal infections caused by <i>Candida</i> species. For example, in a Phase 2b study in subjects with recurrent VVC (RVVC), subjects in the 12-week VT-1161 treatment group (150 mg VT-1161 once daily for 7 days followed by 150 mg VT-1161 once weekly for 11 weeks) showed a 4.8% recurrence rate through Week 48 compared with a 52% recurrence rate in the placebo group in the intent-to-treat analysis. RVVC, defined as 3 or more acute VVC episodes over a 12-month period, is experienced by 5 to 7 million women each year in the US. <i>Candida albicans</i> is the leading cause of recurrent vulvovaginal yeast infections in the United States. However, there has been an increasing trend in the number of vaginal yeast infections attributable to non-albicans species such as <i>C. glabrata</i> and <i>C. tropicalis</i> . In addition to the use of topical products to treat VVC, the majority of the women visiting healthcare professionals receive fluconazole for the treatment of each acute episode. A smaller percentage are prescribed a fluconazole maintenance regimen although fluconazole is not currently approved for the treatment of RVVC. Since some of the <i>C. albicans</i> and the majority of non-albicans isolates are resistant to fluconazole, the management of RVVC has become even more challenging. In both nonclinical studies and clinical trials conducted to date, VT-1161 has demonstrated a favorable safety and tolerability profile, with no discernable adverse effect on liver function. In reproductive toxicity studies in pregnant rats or rabbits, VT-1161 was not teratogenic at any exposure studied. In a recent CYP3A4 drug-drug interaction study utilizing midazolam as the substrate, no clinically significant inhibition and only weak induction of midazolam metabolism was observed. These data are favorable when compared to other oral antifungal agents such as fluconazole. This study is to evaluate the efficacy and safety of VT-1161 compared to fluconazole in treating acute VVC infections in RVVC subjects.

Objectives:

Primary:

- To evaluate the efficacy of oral VT-1161 in the prevention of culture-verified acute episodes of VVC through Week 50 in RVVC subjects.
- To compare the efficacy of oral VT-1161 and fluconazole in the treatment of an acute VVC episode in RVVC subjects.

Secondary:

- To evaluate the safety and tolerability of oral VT-1161 through Week 50.

Methodology:

Study Design:

This is a Phase 3, multicenter, randomized, double-blind study to evaluate the efficacy and safety of VT-1161 oral capsules versus fluconazole in the treatment of acute vulvovaginal candidiasis episodes in subjects with recurrent vulvovaginal candidiasis. In addition, the study will evaluate the efficacy of oral VT-1161 compared to placebo in the prevention of RVVC through Week 50 after treating the acute episodes of VVC with treatment of VT-1161 or fluconazole. Approximately 180 subjects will be randomized, 120 subjects in the VT-1161 arm and 60 subjects in the fluconazole and placebo arm.

Subjects must have a history of RVVC, defined as at least 3 episodes of acute VVC in the past 12 months, as described below:

- Subjects must have an acute VVC episode at the time of Screening, with a documented positive potassium hydroxide (KOH) performed at the investigative site
- Subjects must also have had 2 or more additional episodes of acute VVC in the past 12 months, with at least 1 of the episodes documented by a positive confirmatory laboratory test (i.e., culture, PCR, Affirm test, KOH test, a documented Papanicolaou (Pap) test, or other approved diagnostic tests)

Subjects must also have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥ 3 .

The study consists of two Phases:

1) an Induction Phase for the treatment of the acute VVC episode in which subjects will be randomized to receive one of the following:

- 600 mg VT-1161 (4 x 150 mg capsules) on Day 1 and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2, or
- 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole.

2) a Maintenance Phase in which subjects initially randomized to receive VT-1161 in the Induction Phase will receive 150 mg VT-1161 (1 x 150 mg capsule) weekly for 11 weeks and will then enter a 37-week follow-up period. Subjects randomized to receive over-encapsulated fluconazole in the Induction Phase will receive placebo weekly for 11 weeks and will then enter a 37-week follow-up period.

Once subjects have provided informed consent or assent (for those ages 12-17) the investigational site

will evaluate all subjects by completing a review of pertinent medical history, obtaining vital signs, weight and height, electrocardiogram (ECG) and laboratory tests, reviewing clinical signs and symptoms of vulvovaginitis, performing a complete physical examination including speculum examination of the vagina, performing a KOH wet mount test from a vaginal smear to confirm the presence of yeast, and collecting vaginal swabs to establish a baseline culture for identification of fungal species. Eligible subjects must have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥ 3 and a positive local KOH wet mount preparation from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells, and must meet other initial entry criteria. Once eligibility is confirmed, subjects will be randomized to enter the Induction Phase.

At Screening (Day 1), subjects presenting with an acute infection and meeting all study eligibility criteria will enter the Induction Phase where they will be randomized 2:1 ratio to receive either 600 mg VT-1161 (4 x 150 mg capsules) on Day 1 and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2, or 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole. Subjects will return approximately 14 days after the first dose of VT-1161 or over-encapsulated fluconazole to determine if the acute VVC infection has resolved (defined by a signs and symptoms score of < 3). If the acute VVC has not resolved, the subject will be considered a screen failure and encouraged to see their physician for follow-up care.

All subjects in which the acute VVC infection has resolved will continue into a Maintenance Phase. Subjects initially randomized to receive VT-1161 in the Induction Phase will receive 150 mg VT-1161 (1 x 150 mg capsule) weekly for 11 weeks and will then enter a 37-week follow-up period. Whereas subjects randomized to receive over-encapsulated fluconazole in the Induction Phase will receive placebo weekly for 11 weeks and will then enter a 37-week follow-up period.

Subject's Day 1 (Screening) is defined as the first day of investigational medicinal product (IMP) administration and subsequent study days are defined by the number of consecutive days thereafter. Subject's Day 14 is defined as the first day of weekly dosing of IMP administration.

Study Duration:

The study duration is expected to be approximately 18 months from screening of the first subject until last follow-up of the last subject.

Subject Participation:

The duration of individual subject participation will be approximately 50 weeks. See [Table 1 for the Schedule of Assessments and Procedures](#) which will be performed. After Screening, subjects will return to the clinic on Day 14 (± 2 days), the start of the Maintenance Phase. Subjects will then have visits on Weeks 8 (± 7 days), 14 (± 14 days) (end of treatment [EOT]), 20 (± 14 days), 26 (± 14 days), 32 (± 14 days), 38 (± 14 days), 44 (± 14 days) and 50 (± 14 days) (end of study [EOS]). Subjects who return to the clinic for a recurrent acute VVC episode should be evaluated as per the unscheduled visit noted in the Schedule of Assessment and Procedures.

Scoring of Vulvovaginal Signs and Symptoms:

Vulvovaginal signs and symptoms will be evaluated at Screening and at each subsequent study visit. Each of the following vulvovaginal signs and symptoms will be scored and the individual scores combined, for a maximum score of 18 using the following scale:

- a. Signs: erythema, edema, and excoriation
- b. Symptoms: itching, burning, and irritation

Scoring Scale: Each score should be graded on a scale of 0 to 3 as follows:

- 0 = none (complete absence of any sign or symptom)
- 1 = mild (slight)
- 2 = moderate (present)
- 3 = severe (marked, intense)

Mycology Assessment:

A local mycological assessment using KOH wet mount followed by microscopy will be evaluated at the Screening (Day 1) and at any study visit where a recurrent acute VVC episode is suspected. In addition, a vaginal swab for culture testing will be obtained and sent to the central mycology laboratory at the Screening and each subsequent study visit.

Plasma Pharmacokinetics:

Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects at Day 14, Week 14 and Week 50 visits.

Intense sampling will be obtained from approximately 12 consenting subjects at participating sites on Day 1 and on Day 2, at time points predose and 1, 2, 4, and 8 hours after dosing.

Safety:

Subject safety will be monitored by collection of adverse events (AEs), changes in vital signs, physical and vaginal exam parameters, ECGs, and safety laboratory parameters, including pregnancy tests for women of childbearing potential (WOCBP).

Concomitant Medications:

The following prescription and over-the-counter drug products are prohibited during the study and will be considered a protocol deviation:

1. Topical or oral antifungal drugs (with the exception of fluconazole when prescribed by the Investigator to treat a subject with a recurrent VVC episode. If subject fails to respond to fluconazole treatment, the Investigator may employ treatment options corresponding to the site's standard of care treatment to treat the infection upon consult with the Medical Monitor.)
2. Topical products applied to the vulva or vagina (e.g. antibiotic, antitrichomonal, corticosteroids, or anti-inflammatory agents).
3. Oral antibacterial or antitrichomonal agents for the treatment of bacterial vaginosis, trichomonas, or other concomitant infection unless prescribed by the Investigator.
4. Oral or injectable corticosteroid or immunosuppressive drugs for the duration of the study. Use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, or intraarticular and intralesional

steroids is permitted.
5. Drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).
Number of Subjects (Planned): Approximately 180 randomized subjects are planned for this study. Assuming a 20% discontinuation rate for the duration of the study, approximately 144 subjects are expected to complete the study.
Criteria for Inclusion and Exclusion: <u>Criteria for Inclusion:</u> 1. Subjects must be generally healthy, post-menarchal females 12 years of age and older as of Screening (Day 1). 2. Subjects must have a history of recurrent VVC as defined by three (3) or more episodes of acute VVC in the past 12 months, including the episode confirmed at Screening, with at least one episode (not including the current episode) documented by a positive culture, PCR, Affirm test, KOH test, or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells. 3. Subjects must have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥ 3 and a positive KOH wet mount preparation from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells. 4. Subjects must have a composite vulvovaginal signs and symptoms score of < 3 at the Day 14 Visit. 5. Subjects must have a documented Pap test results at Screening or within the current standard of care guidelines for the appropriate age requirement, reported as either "negative for intraepithelial lesion or malignancy" or "ASCUS-atypical squamous cells of undetermined significance" (not applicable to subjects with a history of total hysterectomy). 6. Subjects must be suitable candidates for oral therapy and be able to swallow capsules intact. 7. Subjects must be willing and able to provide written informed consent or assent (for those ages 12-17) and authorization for use of protected health information. 8. Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned. 9. Subjects of non-childbearing potential must meet the requirements defined below: a. Pre-menopausal with documentation of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) at least 3 months prior to study entry. b. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments at Screening. 10. Subjects of childbearing potential (includes ages 12-17) must use 1 of the following methods of contraception during the study through Week 50: OPTION 1 - Highly effective methods that can be used alone: 1. Copper intrauterine device used continuously and successfully for at least 90 days prior to first dose of study drug^a 2. Levonorgestrel-releasing intrauterine system used successfully for at least 90 days prior to first dose of study drug^a 3. Progestin implant used successfully for at least 90 days prior to first dose of study drug^a

4. Monogamous with a vasectomized male partner (vasectomy performed at least 6 months prior to first dose of study drug)^a 5. Abstinence^b OPTION 2 – Acceptable first and second barrier methods to be used in combination: FIRST (Hormonal Contraception)^a 1. Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring used successfully for at least 90 days prior to first dose of study drug 2. Progestin only oral contraceptives or injection used successfully for at least 90 days prior to first dose of study drug SECOND (Barrier Method) 1. Diaphragm (with spermicide) 2. Cervical cap (with spermicide) 3. Male condom (with or without spermicide) In addition to OPTIONS 1 and 2, subjects of childbearing potential (includes ages 12-17) may also use 1 of the following methods of contraception after completing the Induction Phase on Study Day 14 through Week 50: OPTION 3 (Day 14 – Week 50)^c – Acceptable first and second barrier methods to be used in combination: FIRST (Barrier Method) 1. Diaphragm (with spermicide) 2. Cervical cap (with spermicide) SECOND (Barrier Method) 1. Male condom (with or without spermicide) ^a Subjects who started using an intrauterine device or any of the hormonal contraceptive methods described above less than 3 months prior to the first dose of study medication must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 3 months after start of the use of the IUD or hormonal contraceptive. Similarly, subjects that claim a monogamous relationship with a vasectomized male partner where the vasectomy was performed less than 6 months prior to the first dose of study medication, must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 6 months after the date of the vasectomy. ^b Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and where this is the usual life style of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception. ^c Because of the teratogenic risk associated with repeat dosing of fluconazole, OPTION 3 contraceptive methods cannot be used during Screening and the Induction Phase of the study [from Screening (Day 1) until Day 14 of the study]. Criteria for Exclusion: 1. Subjects must not have the presence of concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, <i>Trichomonas vaginalis</i>, <i>Chlamydia trachomatis</i>, or <i>Neisseria gonorrhoeae</i>) at Screening (Day 1) visit. 2. Subjects must not have an active HPV infection as evidenced by visible condylomas on vulvovaginal examination at Screening (Day 1) visit. 3. Subjects must not have the presence or a history of another vaginal or vulvar condition(s) that in

- the Investigator's opinion would confound the interpretation of clinical response.
4. Subjects must not have a history of cervical cancer.
 5. Subjects must not use any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to Screening visit; nor use of topical vulvar or vaginal steroids during the study or within 7 days prior to Screening visit. However, use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, collunarium/nasal, intraarticular and intralesional steroids is permitted.
 6. Subjects must not use any systemic (e.g., oral or injectable) or topical (applied to the vulva or vaginal area) antifungal, antibacterial, or antitrichomonal drugs for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection during the study (unless prescribed by the Investigator) or within 7 days prior to Screening.
 7. Subjects must not be using drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 during the study (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).
 8. Subjects must not use any vaginal estrogen replacement therapy, ospemifene, Vitamin E gel capsules (vaginally) or lubricants within 7 days prior to Screening.
 9. Subjects must not have a condition that would require treatment during the study with concomitant topical (applied to vulva and vagina) or systemic antimicrobial therapy for any reason.
 10. Subjects must not have received an immunosuppressive medication (e.g. cyclosporine, tacrolimus, methotrexate, 6-mercaptopurine, mycophenolate, etc.), or radiation therapy within 3 months prior to Screening or have a medical condition where it would be likely that the subject may need to use these therapies during the study.
 11. Subjects must not have evidence of any clinically significant major organ disease or current clinically significant infection or any other conditions (with the exception of acute VVC) that may affect the clinical assessment of RVVC per investigator judgment.
 12. Subjects must not have any comorbid condition that in the opinion of the Investigator would preclude the safe participation of the subject in the study or would prevent the subject from meeting the study requirements.
 13. Subjects must not have any condition that in the opinion of the investigator could impact drug absorption (e.g. gastrectomy, Roux-en-Y gastric bypass surgery, gastric bands or staples, etc.), distribution, or elimination.
 14. Subjects must not have poorly controlled diabetes mellitus (HbA1c $\geq$ 8.5% at Screening; performed only on known diabetics or subjects suspected to have diabetes by the investigative site).
 15. Subjects must not have moderate or severe hepatic and/or renal disease (defined in [Appendix B](#) and [Appendix C](#)).
 16. Subjects must not have a laboratory abnormality that in the opinion of the Investigator is likely to introduce additional risk to the subject or might interfere with data interpretation. The specific findings listed below are excluded at Day 1 (a single repeat laboratory evaluation is allowed for eligibility determination, except for HIV, HBsAg and antibodies to hepatitis C virus):
 - a. Serum alanine aminotransferase (ALT) $\geq$ 2.0x the upper limit of normal (ULN) of the reference range.
 - b. Serum aspartate aminotransferase (AST) $\geq$ 2.0x the ULN of the reference range.
 - c. Serum total bilirubin $\geq$ 1.5x the ULN of the reference range, unless the elevation is consistent with Gilbert's Syndrome.
 - d. Electrocardiographic QTc interval $>$ 470 msec as corrected by the Fridericia formula, or any clinically significant electrocardiographic abnormality.

- e. Positive test for antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibodies to hepatitis C virus.
17. Subjects of childbearing potential must not be pregnant (positive pregnancy test at Screening), lactating, or planning to become pregnant during the study period.
 18. Subjects must not have planned surgery or other medical procedures that in the Investigator's opinion would impact compliance with the protocol.
 19. Subjects must not have active substance abuse (e.g., drugs of any kind, including alcohol) or any other medical, psychiatric or social condition that in the Investigator's opinion would preclude compliance with the protocol.
 20. Subjects must not have received VT-1161 study medication in a previous study.
 21. Subjects must not have received any IMP in a clinical trial within 5 half-lives of that IMP prior to Screening (if unknown, 60 days prior to Screening).
 22. Subjects must not have a known history of intolerance or hypersensitivity to azole antifungal drugs (e.g., fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole), or any excipients of the capsule formulation.

Induction Treatment Phase

Investigational Medicinal Product: VT-1161 150 mg capsules

Dose and Mode of Administration:

Oral administration of 600 mg VT-1161 (4 x 150 mg capsules) on Day 1, and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2.

Oral administration of IMP within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Placebo capsules matching the VT-1161 capsules will be administered on Day 1 (4 capsules) and Day 2 (3 capsules) to maintain study blind for those subjects randomized to the fluconazole treatment arm.

Investigational Medicinal Product: Fluconazole 150 mg tablets, over-encapsulated

Dose and Mode of Administration:

Oral administration of 3 sequential doses (every 72 hours) of fluconazole 150 mg starting on Day 1.

Oral administration of IMP within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Placebo capsules matching the over-encapsulated fluconazole IMP will be administered on Day 1, 4 and 7 to maintain study blind for those subjects randomized to the VT-1161 treatment arm.

Maintenance Treatment Phase

Maintenance Phase Test Product: VT-1161 150 mg capsules

Dose and Mode of Administration:

Oral administration of VT-1161 within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Starting on Day 14, VT-1161 150 mg (1 capsule) will be given once weekly for 11 weeks. <u>Duration of Administration:</u> 11 weeks Maintenance Phase Reference Product: Matching Placebo capsules <u>Dose and Mode of Administration:</u> Oral administration of placebo within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose. Starting on Day 14, placebo (1 capsule) will be given once weekly for 11 weeks. <u>Duration of Administration:</u> 11 weeks
Study Populations: <u>Intent-to-Treat (ITT) Population:</u> All randomized subjects. <u>Safety Population:</u> All randomized subjects who received at least 1 dose of study drug. <u>Per Protocol Population (PP):</u> All randomized subjects who had the following: • Had no deviations to inclusion/exclusion criteria that could impact treatment outcome. • Were compliant with the assigned study treatment, defined as $\geq 80\%$ compliance during the Induction Phase and $\geq 50\%$ compliance during the Maintenance Phase. • Had the Week 50 visit completed within the acceptable time window (± 14 days). • Had no major protocol violations that would impact treatment outcome. <u>Modified ITT:</u> All enrolled subjects who had the following: • Positive KOH at Screening. • Positive culture at Screening. • Negative culture at Day 14.
Criteria for Evaluation: <u>Efficacy:</u> Clinical and mycological assessments will be conducted as outlined in Table 1. Schedule of Assessments and Procedures. All efficacy analyses will be performed on the ITT, PP, and mITT Populations. The primary efficacy outcome measure is the proportion of subjects with one or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT population, which will include the subjects who failed clearing their infection during the Induction Phase. An acute VVC episode (considered a recurrent episode) is defined as a positive culture for <i>Candida</i> species and a clinical signs and symptoms score of ≥ 3. The key secondary efficacy outcome measures include the following:

- a. The proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole.
- b. The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms of ≥ 3 during the Maintenance Phase (post Day 14 through Week 50).
- c. Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥ 3 during the Maintenance Phase (post Day 14 through Week 50).
- d. The proportion of subjects with at least one positive culture for *Candida* during the Maintenance Phase.

Safety:

All safety analyses will be performed on the Safety Population. AEs will be collected throughout the study. Physical and vaginal examination findings and vital signs will be recorded at Screening and throughout the study per Table 1.

Schedule of Assessments and Procedures.

ECGs and safety laboratory tests (hematology, chemistry, and urinalysis) will be obtained throughout the study. All concomitant medications taken during the period from 30 days prior to Screening through the Week 50 (EOS) visit will be recorded in the case report form (CRF). Pertinent and all major medical conditions will be recorded on the Medical History CRF.

Subjects who want to discontinue from the study should be encouraged to remain in the study for all remaining visits through Week 50 for safety and efficacy assessments. All subjects who discontinue early from the study should have all EOS procedures performed on the day of discontinuation.

Statistical Methods and Data Analysis:

A statistical analysis plan will be finalized before 50% of subjects are enrolled.

Efficacy Analysis:

The statistical objectives of this study will be:

1. To determine if there is a difference in the proportions of subjects with one or more episodes of culture-verified acute VVC in those receiving VT-1161 compared to those receiving placebo
2. To determine if there is a difference in the ability of VT-1161 and fluconazole to resolve acute episodes in subjects with RVVC.

A sample size of 82 subjects in the VT-1161 arm and 41 subjects in the fluconazole/placebo arm provides at least 90% power to detect a treatment difference between the VT-1161 treatment group and the fluconazole /placebo treatment group with a type 1 error rate of 0.05. Sample size calculation assumes 50% of the subjects in the placebo arm will have at least one culture-verified acute VVC episode post-randomization through Week 50. For the first key secondary endpoint, the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole, a sample size of 120 subjects in the VT-1161 arm and 60 subjects in the fluconazole/placebo arm provides at least 88% power to detect non-inferiority between the VT-1161 treatment group and the fluconazole treatment group with a non-inferiority margin of 15% and a type 1 error rate of 0.05. The sample size calculation assumes that 90% of the subjects in the fluconazole arm will resolve their acute VVC infection by Day 14.

For the efficacy analyses, missing values for the investigator's assessment of clinical signs and symptoms or the culture result will be imputed using the method of multiple imputation. For subjects who discontinue the study early and have missing assessments for all visits after discontinuation, the missing

values for the expected scheduled visits will be imputed using the method of multiple imputation. The missing values will be imputed using the following auxiliary information: region, treatment, baseline BMI, baseline age, ethnicity, and visit.

A chi-square test will be used to compare the proportion of subjects with one or more culture-verified acute VVC in those receiving VT-1161 compared to those receiving fluconazole and placebo. The proportion of subjects who have cleared their infection at Day 14 in those receiving VT-1161 will be evaluated for non-inferiority versus those receiving fluconazole utilizing a non-inferiority margin of 15%.

Safety Analysis:

AEs will be coded using the Medical Dictionary for Regulatory Activities® dictionary. The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by system organ class, preferred term, and greatest severity with a breakdown by treatment group. Mean changes from pre-treatment in vital signs, ECG, and clinical laboratory variables will be summarized by treatment group.

Pharmacokinetics:

No formal statistical hypothesis testing related to pharmacokinetics will be conducted. VT-1161 concentrations will be presented by visit with descriptive statistics. The pharmacokinetic data will be used in a cross-population pharmacokinetic analysis that will be presented in a separate report.

Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects prior to IMP on Day 14 and Week 14 and at Week 50. Intense sampling will be obtained only from consenting subjects at participating sites on Day 1 and Day 2 (predose and 1, 2, 4, and 8 hours after dosing, with ±10-minute window per timepoint).

Table 1. Schedule of Assessments and Procedures

Activities	Screening (Day 1)	Day 2 ¹	Day 14 (±2 days) Initial TOC	Week 8 (±7 days)	Week 14 (±14 days) EOT	Week 20 (±14 days)	Week 26 (±14 days)	Week 32 (±14 days)	Week 38 (±14 days)	Week 44 (±14 days)	Week 50 (±14 days) EOS	Unscheduled Visit ¹
Sign Informed Consent or Assent Form	X											
Inclusion/Exclusion Criteria	X											
Medical/Surgical History	X											
Prior/Concomitant Medications/Treatments ^a	X	X	X	X	X	X	X	X	X	X	X	X
Collect and Record AEs		X	X	X	X	X	X	X	X	X	X	X
Body Height and Weight	X				X ^b		X ^b				X ^b	
Vital Signs ^c	X		X	X	X	X	X	X	X	X	X	X
Physical and Vaginal Examination	X		X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d	X ^d
Clinical Signs and Symptoms of Vulvovaginitis	X		X	X	X	X	X	X	X	X	X	X
Local KOH Wet Mount	X											X
Central Vaginal Fungal Culture	X		X	X	X	X	X	X	X	X	X	X
ECG	X		X		X		X				X	
PK Samples ^e	X	X	X		X						X	
Clinical Laboratory Samples ^f	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X		X	
Hematology (CBC with differential)	X		X		X		X		X		X	
HIV Ab, HBsAg, anti-HCV	X											
Pregnancy Test ^g (WOCBP)	X				X		X				X	
Randomization	X											
Administer VT-1161 or Fluconazole ^h	X	X										
Administer VT-1161 or Placebo			X									
Review IMP ^h			X	X	X							

Abbreviations: AEs: adverse events; CBC: complete blood count; ECG: electrocardiogram; EOS: End of Study; EOT: End of Treatment; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; IMP: investigational medicinal product; KOH: potassium hydroxide prep; PK: pharmacokinetic; TOC: Test of Cure; WOCBP: women of childbearing potential.

NDA 215888
Vivjoa (oteseconazole)

- a. All medication taken 30 days prior to Screening and all non-pharmacologic treatments received 72 hours prior to Screening will be recorded through the EOS visit.
- b. Weight only.
- c. Vital signs include sitting heart rate, blood pressure, temperature, and respiratory rate.
- d. Limited physical examination, i.e. vaginal speculum examination plus a symptom directed physical examination.
- e. Subjects participating in the intense Day 1 and Day 2 PK collection will have samples taken predose and 1, 2, 4, and 8 hours after dosing. All subjects will have PK draws prior to IMP on Day 14 and Week 14 and at Week 50.
- f. Serum chemistry (creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, conjugated bilirubin, albumin, total protein, total carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus, creatine phosphokinase [CK], cholesterol and triglycerides). Testing for HbA1c is performed only in known or suspected diabetic subjects at Screening. Cultures to test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* will be taken at Screening and sent to the central lab. Testing for *bacterial vaginosis* will be done locally at Screening. An OSOM® Rapid test or similar test will be performed for *Trichomonas vaginalis* locally at Screening.
- g. For WOCBP, a local lab urine and central lab serum pregnancy test will be obtained at the Screening Day 1 visit. A central lab serum pregnancy test will be performed at Weeks 14, 26, and 50.
- h. IMP is to be administered within 30 minutes after the subject's main meal of the day (as determined by the subject) at approximately the same time of the day consistently throughout the study. Approximately 240 mL (approx. 8 oz.) of water is to be consumed with each dose of IMP.
Subject will be randomized to receive either 600 mg VT-1161 (4 x 150 mg capsules) on Day 1 and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2 followed by 11 weekly doses of 150 mg VT-1161, or 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole followed by 11 weekly doses of placebo. In the Induction Phase, IMP may be over-encapsulated and matching placebo capsules will be provided to maintain study blind. Subjects participating in the intense PK collection will be required to take the Days 1 and 2 IMP at the Investigational site.
Remind subject to bring IMP to each visit to assess compliance.
- i. Only subjects participating in the intense PK will come in for the Day 2 visit.
- j. All procedures listed are to be completed only for unscheduled visits where a recurrent VVC episode is suspected. If the unscheduled visit is for repeat procedures (i.e., ECG, safety labs, etc.), only those specific procedures need to be performed, along with collection of any changes in medical treatments or medications and collection of any AEs.

16. Efficacy: Additional Information and Assessment

16.1. Additional Analyses for Study CL-011

Screening Characteristics for Study CL-011

[Table 150](#) summarizes key screening signs and symptoms and microbiologic characteristics of the ITT population. Note that randomization had not occurred at the time of screening. This analysis looks back at the screening period to determine what characteristics these subjects had. Additionally, this information does not include the subjects who entered into the screening phase but were not randomized.

At screening the placebo arm had a numerically higher signs and symptoms score compared to the oteseconazole arm. *Candida albicans* accounted for the majority of screening pathogens in both arms (51.6% in the oteseconazole and 49.5% in the placebo), followed by *C. glabrata* (4.6% and 7.3%, respectively). There were no mixed *Candida* pathogens. A sizeable percentage of subjects in each arm had negative *Candida* cultures at screening, 38% and 35%, respectively.

Table 150. Trial CL-011 Screening Signs and Symptoms and Microbiologic Characteristics, ITT Population

Screening	Oteseconazole (N=217)	Placebo (N=109)	Total (N=326)
Screening signs and symptoms score			
Mean (SD))	8.3 (3.50)	9.0 (3.42)	8.5 (3.48)
Median (min, max)	8.0 (3, 17)	9.0 (3, 18)	8.0 (3, 18)
Screening signs and symptoms score, by category			
3-6	86 (39.6)	28 (25.7)	114 (35.0)
7-12	92 (42.4)	63 (57.8)	155 (47.5)
13-18	39 (18.0)	18 (16.5)	57 (17.5)
Screening culture results			
Positive for <i>Candida</i>	125 (57.6)	66 (60.6)	191 (58.6)
Negative for <i>Candida</i>	83 (38.2)	38 (34.9)	121 (37.1)
Missing/Unknown	9 (4.1)	5 (4.6)	14 (4.3)
Pathogen at screening			
Of those positive for <i>Candida</i>			
<i>Candida albicans</i>	112 (51.6)	54 (49.5)	166 (50.9)
<i>Candida glabrata</i>	10 (4.6)	8 (7.3)	18 (5.5)
<i>Candida lusitanae</i>	2 (0.9)	1 (0.9)	3 (0.9)
<i>Candida tropicalis</i>	1 (0.5)	0	1 (0.3)
<i>Candida dubliniensis</i>	0	1 (0.9)	1 (0.3)
<i>Candida sphaerica</i>	0	1 (0.9)	1 (0.3)
<i>Candida krusei</i>	0	1 (0.9)	1 (0.3)
Of those negative for <i>Candida</i>			
<i>Saccharomyces cerevisiae</i>	1 (0.5)	1 (0.9)	2 (0.6)
<i>Stephanoascus ciferrii</i>	3 (1.4)	0	3 (0.9)
Unknown	79 (36.4)	37 (33.9)	116 (35.6)

	Oteseconazole (N=217)	Placebo (N=109)	Total (N=326)
Screening			
Screening KOH smear			
Positive	165 (76.0)	94 (86.2)	259 (79.4)
Missing/unknown	52 (24.0)	15 (13.8)	67 (20.6)
Screening gram stain			
Missing/unknown	195 (89.9)	102 (93.6)	297 (91.1)
Positive	22 (10.1)	7 (6.4)	29 (8.9)

Source: Reviewer verified numbers in the table using ADSL.xpt.
Abbreviations: ITT, intent to treat; KOH, potassium hydroxide.

Subgroup Analyses of the Primary Endpoint for Study CL-011

The subgroup analyses results for the primary endpoint based on the MI (multiple imputation) method and analysis method of missing counted as failures are summarized in [Table 151](#).

The proportion of subjects with ≥ 1 culture-verified acute VVC episodes during the Maintenance Phase by age group, race, ethnicity, country, Day 1 signs and symptoms score (0, 1, and 2) and number of historic VVC episodes 4 or more were analyzed. The proportion of subjects with ≥ 1 culture-verified acute VVC episodes during the Maintenance Phase was significantly lower in oteseconazole as compared to placebo except Black or African American, Poland and Day 1 signs and symptoms score =2 in the analysis method of missing counted as failures.

Table 151. Subgroup Analyses of Primary Endpoint Trial CL-011: ITT Population

Subgroup	Oteseconazole (N=217)	Placebo (N=109)	P-value
Age group			
18-33 Years	N=109	N=54	<0.001
Average % (MI) ^a	4.9	49.3	<0.001
No. recurrence (%) ^b	27 (24.8)	34 (63.0)	<0.001
≥ 34 years	N=107	N=55	
Average % (MI)	7.7	36.5	<0.001
No. recurrence (%)	40 (25.6)	40 (50.0)	<0.001
Race			
White	N=156	N=80	
Average % (MI) ^a	6.0	39.1	<0.001
No. recurrence (%) ^b	40 (25.6)	40 (50.0)	<0.001
Black or African American	N=26	N=17	
Average % (MI) ^a	19.6	47.1	0.054
No. recurrence (%) ^b	13 (50.0)	8 (47.1)	<0.001
Other	N=35	N=12	
Average % (MI) ^a	0.3	61.7	<0.001
No. recurrence (%) ^b	3 (8.6)	8 (66.7)	<0.001
Ethnicity			
Hispanic or Latino	N=19	N=6	
Average % (MI) ^a	11.6	68.3	<0.001
No. recurrence (%) ^b	5 (26.3)	5 (83.3)	0.013
Not Hispanic	N=198	N=103	
Average % (MI) ^a	6.2	41.4	<0.001
No. of recurrence (%) ^b	51 (25.8)	51 (49.5)	<0.001
Country			
Bulgaria	N=50	N=23	
Average % (MI) ^a	6.2	10.9	0.533
No. recurrence (%) ^b	11 (22.0)	7 (30.4)	0.437
Canada	N=8	N=8	

Subgroup	Oteseconazole (N=217)	Placebo (N=109)	P-value
Average % (MI) ^a	0.0	75.0	NA
No. recurrence (%) ^b	1 (12.5)	6 (75.0)	0.012
Japan	N=32	N=12	
Average % (MI) ^a	0.3	61.7	<0.001
No. recurrence (%) ^b	3 (27.3)	8 (66.7)	<0.001
Poland	N=33	N=24	
Average % (MI) ^a	6.1	32.5	0.011
No. recurrence (%) ^b	10 (30.3)	12 (50.0)	0.132
United Kingdom	N=9	N=3	
Average % (MI) ^a	11.1	66.7	NA
No. recurrence (%) ^b	4 (44.4)	2 (66.7)	0.505
United States	N=85	N=39	
Average % (MI) ^a	9.8	53.8	<0.001
No. recurrence (%) ^b	27 (31.8)	21 (53.9)	0.019
Day 1 signs and symptom score			
0	N=119	N=75	
Average % (MI) ^a	7.1	37.6	<0.001
No. recurrence (%) ^b	30 (25.2)	34 (45.3)	0.004
1	N=51	N=21	
Average % (MI) ^a	5.9	43.8	<0.001
No. recurrence (%) ^b	13 (25.5)	11 (52.4)	<0.001
2	N=45	N=13	
Average % (MI) ^a	6.7	71.5	<0.001
No. recurrence (%) ^b	11 (24.4)	11 (84.6)	<0.001
Number of historic VVC episode			
0-3	N=120	N=54	
Average % (MI) ^a	7.7	36.5	<0.001
No. recurrence (%) ^b	30 (25.0)	25 (46.3)	0.005
≥ 4	N=97	N=55	
Average % (MI) ^a	5.5	49.1	<0.001
No. recurrence (%) ^b	26 (26.8)	31 (56.4)	<0.001

Source: Adapted from Table 14.2.1.6 and conducted analyses by reviewer using ADEFF dataset

a. Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

b. Subjects with incomplete follow-up had their missing values imputed as failures.

The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Abbreviations: ITT, intent to treat; MI, multiple imputations; NA, not applicable; VVC, vulvovaginal candidiasis.

Results of Analyses of Selected Secondary Endpoints for Study CL-011

The secondary endpoints results of the proportion of subjects with ≥ 1 positive culture for *Candida* species during the Maintenance Phase and the proportion of subjects with ≥ 1 culture-verified acute VVC episode during post randomization through Week 24 for ITT population are summarized in [Table 152](#).

The proportion of subjects with ≥ 1 positive culture for *Candida* species during the Maintenance Phase was significantly lower for oteseconazole compared to placebo using both methods for handling missing data. The average percentage of subject with ≥ 1 positive culture for *Candida* species during the Maintenance Phase was 29.4% in oteseconazole and 64.2% in placebo using the MI method. It should be noted that these values are much higher than those observed for the primary endpoint of ≥ 1 culture-verified acute VVC episode during the Maintenance Phase ([Table 12](#)). This indicates that there were many asymptomatic subjects with a positive culture which could indicate colonization rather than actual infection.

The proportion of subjects with ≥ 1 culture-verified acute VVC episode during post randomization through Week 24 was significantly lower for oteseconazole compared to placebo using both methods for handling missing data.

Table 152. Proportion of Subjects With ≥ 1 Positive Culture for *Candida* Species During the Maintenance Phase and Proportion of Subjects With ≥ 1 Culture Verified Acute VVC Episode Through Week 24 for Trial CL-011: ITT Population

Analysis Method	Oteseconazole N=217	Placebo N=109
≥ 1 Positive culture for <i>Candida</i> through Week 24		
MI (average %)*	29.4	84.2
Min, max	27.6, 33.6	81.7, 87.2
P-value	<0.001	
Missing as failures**	100 (46.1)	92 (84.4)
P-value#	<0.001	
≥ 1 Culture-verified acute VVC Episode through Week 24		
MI (average %) *	3.3	37.4
Min, max (%)	3.2, 3.7	36.7, 38.5
P-value	<0.001	
Missing as failures**	32 (14.8)	49 (45.0)
P-value#	<0.001	

Source: Adapted from Table 14.2.2.2.1 and 14.2.2.3.1 and conducted analyses by reviewer using ADEFF dataset

*:Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

**:. Subjects with incomplete follow-up had their missing values imputed as failures.

#The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Abbreviations: ITT, intent to treat; VVC, vulvovaginal candidiasis.

The 36-item short form survey (SF-36) mental component score (MCS) and total score mean changes from screening through Week 48 are summarized in [Table 153](#). Both MCS and total score changes were small and similar between the two groups. The mean differences for SF-36 MSC and total score were 2.05 (-1.5, 5.6) and 2.0 (-1.1, 5.1), respectively.

Table 153. SF MSC and Total Score Change From Screening Through Week 48 for Trial CL-011:ITT Population

Analysis Method	Oteseconazole N=217 n (%)	Placebo N=109 n (%)
SF-36 MCS		
Screening	N=203	N=102
Mean (SD)	77.5 (17.6)	75.3 (17.6)
Week 48	N=200	N=102
Mean (SD)	81.5 (15.7)	79.3 (18.0)
Change from Screening to Week 48	N=199	N=100
LS Mean (SE)	4.7 (1.0)	2.6 (1.5)
95% CI	2.6, 6.7	-0.3, 5.5
LS Mean Difference (95% CI)	2.05 (-1.5, 5.6)	
P-value	0.255	
SF-36 Total Score		
Screening	N=203	N=102
Mean (SD)	80.0 (15.7)	78.8 (15.6)
Week 48	N=200	N=102
Mean (SD)	84.3 (14.2)	82.2 (16.9)
Change from Screening	N=199	N=100
LS Mean (SE)	4.6 (0.9)	2.6 (1.3)
95% CI	2.8, 6.4	0.06, 5.1
LS Mean Difference (95% CI)	2.0 (-1.1, 5.1)	
P-value	0.200	

Source: Adapted from Table 14.2.2.4.1 and Table 14.2.2.5.1 and confirmed by reviewer using ADQS dataset
Abbreviations: ITT, intent to treat; LS, least squares; MCS, mental component score; SE, standard error; SF-36, 36 item short form survey.

16.2. Additional Analyses for Study CL-012

Screening Characteristics for Study CL-012

[Table 154](#) summarizes key screening signs and symptoms and microbiologic characteristics of the ITT population. Note that randomization had not occurred at the time of screening. This analysis looks back at the screening period to determine what characteristics these subjects had. Additionally, this information does not include the subjects who entered into the screening phase but were not randomized.

At screening the placebo arm had a numerically higher signs and symptoms score compared to the oteseconazole arm. *Candida albicans* accounted for the majority of screening pathogens in both arms (46.3% in the oteseconazole and 56.5% in the placebo), followed by *C. glabrata* (4.1% and 6.5%, respectively). There were a few patients with mixed *Candida* pathogens. A sizeable percentage of subjects in each arm had negative *Candida* cultures at screening, 39.4% and 31.5%, respectively.

Table 154. Trial CL-012 Screening Signs and Symptoms and Microbiologic Characteristics, ITT Population

Screening	Oteseconazole (N=218)	Placebo (N=108)	Total (N=326)
Screening signs and symptoms score			
Mean (SD)	8.6 (3.29)	9.1 (3.39)	8.7 (3.32)
Median (min, max)	8.0 (3, 18)	9.0 (3, 16)	9.0 (3, 18)
Screening signs and symptoms score, by category			
>=9	108 (49.5)	60 (55.6)	168 (51.5)
4-8	104 (47.7)	46 (42.6)	150 (46.0)
3	6 (2.8)	2 (1.9)	8 (2.5)
Culture results at screening			
Positive for <i>Candida</i>	120 (55.0)	70 (64.8)	190 (58.3)
Negative for <i>Candida</i>	86 (39.4)	34 (31.5)	120 (36.8)
Missing	12 (5.5)	4 (3.7)	16 (4.9)
Pathogens at screening			
Of those positive for <i>Candida</i>			
<i>Candida albicans</i>	101 (46.3)	61 (56.5)	162 (49.7)
<i>Candida glabrata</i>	9 (4.1)	7 (6.5)	16 (4.9)
<i>Candida albicans</i> , <i>Candida glabrata</i>			
	2 (0.9)	0	2 (0.6)
<i>Candida parapsilosis</i>			
	2 (0.9)	0	2 (0.6)
<i>Candida albicans</i> , <i>Candida lusitanae</i>			
	1 (0.5)	0	1 (0.3)
<i>Candida albicans</i> , <i>Candida tropicalis</i>			
	1 (0.5)	0	1 (0.3)
<i>Candida dubliniensis</i>			
	1 (0.5)	1 (0.9)	2 (0.6)
<i>Candida lusitanae</i>			
	1 (0.5)	0	1 (0.3)
<i>Candida species</i>			
	1 (0.5)	0	1 (0.3)
<i>Candida tropicalis</i>			
	1 (0.5)	0	1 (0.3)
<i>Candida sphaerica</i>			
	0	1 (0.9)	1 (0.3)
Of those negative for <i>Candida</i>			
<i>Saccharomyces cerevisiae</i>	2 (0.9)	1 (0.9)	3 (0.9)
Yeast	3 (1.4)	1 (0.9)	4 (1.2)
<i>Stephanoascus ciferrii</i>	1 (0.5)	0	1 (0.3)
Unknown	80 (36.7)	32 (29.6)	103 (31.6)
Potassium hydroxide results at screening			
Negative	160 (73.4)	73 (67.6)	233 (71.5)
Positive	58 (26.6)	35 (32.4)	93 (28.5)
Gran stain results at screening			
Negative	160 (73.4)	73 (67.6)	233 (71.5)
Positive	58 (26.6)	35 (32.4)	93 (28.5)

Source: Reviewer verified numbers in the table using ADSL.xpt.
Abbreviations: ITT, intent to treat.

Subgroup Analyses of the Primary Endpoint for Study CL-012

The subgroup analysis results for the primary endpoint based on the MI method and missing counted as failures analysis method are summarized in [Table 155](#).

The proportion of subjects with ≥ 1 culture-verified acute VVC episode during the Maintenance Phase by age group, race, ethnicity, country (USA and Czech), Day 1 signs and symptoms score

(0, 1, and 2) and number of historic VVC episodes 4 or more were significantly lower in oteseconazole as compared to placebo except Hispanic or Latino and Hungary, Romania and Ukraine subjects in the missing counted as failure analysis method.

Table 155. Subgroup Analyses of Primary Endpoint Trial CL-012:ITT Population

Subgroup	Oteseconazole (N=218)	Placebo (N=108)	P-value
Age group			
18-33 Years	N=111	N=54	<0.001
Average % (MI) ^a	5.6	35.7	<0.001
No. Recurrence (%) ^b	26 (23.4)	24 (44.4)	0.006
≥34 years	N=107	N=54	
Average % (MI)	2.1	43.1	<0.001
No. Recurrence (%)	20 (18.7)	28 (51.9)	<0.001
Race			
White	N=193	N=96	
Average % (MI) ^a	3.7	37.2	<0.001
No. Recurrence (%) ^b	38 (19.7)	43 (44.8)	<0.001
Black or African American	N=23	N=8	
Average % (MI) ^a	5.7	48.8	0.054
No. Recurrence (%) ^b	8 (34.8)	6 (75.0)	0.049
Other	N=2	N=4	
Average % (MI) ^a	0.0	75.0	NA
No. Recurrence (%) ^b	0	3 (75.0)	NA
Ethnicity			
Hispanic or Latino	N=30	N=18	
Average % (MI) ^a	3.7	31.1	0.009
No. Recurrence (%) ^b	9 (30.0)	7 (38.9)	0.527
Not Hispanic	N=187	N=90	
Average % (MI) ^a	4.0	41.1	<0.001
No. of Recurrence ^b	37 (19.8)	45 (50.0)	<0.001
Country			
Belgium	N=18	N=8	
Average % (MI) ^a	5.6	75.0	0.533
No. Recurrence (%) ^b	1 (5.6)	6 (75.0)	<0.001
Czech Republic	N=51	N=22	
Average % (MI) ^a	5.9	45.5	<0.001
No. Recurrence (%) ^b	5 (9.8)	10 (45.5)	<0.001
Hungary	N=8	N=3	
Average % (MI) ^a	0.0	33.3	<0.001
No. Recurrence (%) ^b	1 (12.5)	1 (33.3)	0.425
Romania	N=44	N=28	
Average % (MI) ^a	2.3	25.7	0.003
No. Recurrence (%) ^b	11 (25.0)	9 (32.1)	0.510
Ukraine	N=17	N=9	
Average % (MI) ^a	0.0	27.8	NA
No. Recurrence (%) ^b	4 (23.5)	5 (55.6)	0.103
United States	N=80	N=38	
Average % (MI) ^a	4.4	41.8	<0.001
No. Recurrence (%) ^b	24 (30.0)	21 (55.3)	0.008

Subgroup	Oteseconazole (N=218)	Placebo (N=108)	P-value
Day 1 Signs and Symptom Score			
0	N=123	N=59	
Average % (MI) ^a	4.3	36.3	<0.001
No. Recurrence (%) ^b	25 (20.3)	23 (39.0)	0.008
1	N=58	N=28	
Average % (MI) ^a	5.2	48.2	<0.001
No. Recurrence (%) ^b	10 (17.2)	16 (57.1)	<0.001
2	N=35	N=21	
Average % (MI) ^a	0.3	36.7	<0.001
No. Recurrence (%) ^b	10 (28.6)	13 (61.9)	<0.001
Number of historic VVC episode			
0-3	N=108	N=48	
Average % (MI) ^a	4.0	43.5	<0.001
No. Recurrence (%) ^b	22 (20.4)	25 (52.1)	0.005
≥ 4	N=110	N=60	
Average % (MI) ^a	3.8	36.2	<0.001
No. Recurrence (%) ^b	24 (21.8)	27 (45.0)	0.002

Source: Adapted from Table 14.2.1.6 and conducted analyses by reviewer using ADEFF dataset

^a Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

^b Missing were imputed as failures

The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Abbreviations: MI, multiple imputations; NA, not applicable; VVC, vulvovaginal candidiasis.

Results of Analyses of Selected Secondary Endpoints for Study CL-012

The secondary endpoint results of the proportion of subjects with ≥ 1 positive culture for *Candida* species during the Maintenance Phase and the proportion of subjects with ≥ 1 culture-verified acute VVC episode during post randomization through Week 24 for ITT population are summarized in [Table 156](#).

The proportion of subjects with ≥ 1 positive culture for *Candida* species during the Maintenance Phase was significantly lower for oteseconazole compared to placebo using both methods for handling missing data. The average percentage of subject with ≥ 1 positive culture for *Candida* species during the Maintenance Phase was 27.6% in oteseconazole and 84.0% in placebo using the MI method. As noted for Study CL-011, these values are much higher than those observed for the primary endpoint of ≥ 1 culture-verified acute VVC episode during the Maintenance Phase ([Table 12](#) indicating many asymptomatic subjects had a positive culture).

The proportion of subjects with ≥ 1 culture-verified acute VVC episode during post randomization through Week 24 was significantly lower for oteseconazole compared to placebo using both methods for handling missing data.

Table 156. Proportion of Subjects With ≥ 1 Positive Culture for *Candida* Species During the Maintenance Phase and Proportion of Subjects With Culture-Verified Acute VVC Episode Through Week 24 for Trial CL-012 : ITT Population

Analysis Method	Oteseconazole N=218 n (%)	Placebo N=108 n (%)
≥ 1 Positive culture for <i>Candida</i> through Week 24		
Average % (MI) ^[1]	27.6	84.0
Min, max	26.6, 28.9	79.6, 86.1
P-value	<0.001	
Missing as failures ^[2]	107 (49.1)	94 (87.0)
P-value ^[3]	<0.001	
≥ 1 Culture-verified Acute VVC episode through Week 24		
Average % (MI) ^[1]	2.8	31.9
Min, max (%)	2.8, 3.2	30.6, 33.3
P-value	<0.001	
Missing as failures ^[2]	35 (16.1)	43 (39.8)
P-value ^[3]	<0.001	

Source: Adapted from Table 14.2.2.2.1 and 14.2.2.3.1 and conducted analyses by reviewer using ADEFF dataset

^[1] Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

^[2] Missing were imputed as failures

^[3] The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Abbreviations: ITT, intent to treat; MI, multiple imputations; VVC, vulvovaginal candidiasis.

The SF-36 MCS and total score and their changes from Screening through Week 48 are summarized in [Table 157](#). Both MCS and total score changes were small and similar between the two groups. The mean differences for SF MSC and Total Score were 2.5 (-1.4, 6.4) and 2.2 (-1.1, 5.6), respectively.

Table 157. SF-36 MCS and Total Score Changes From Screening Through Week 48 for Trial CL-012: ITT Population

Analysis Method	Oteseconazole N=218 n (%)	Placebo N=108 n (%)
SF-36 MCS		
Screening		
Mean (SD)	N=199 71.5 (19.7)	N=100 67.4 (24.5)
Week 48		
Mean (SD)	N=197 84.7 (14.2)	N=101 82.0 (19.1)
Change from Screening to Week 48		
LS Mean (SE)	N=194 12.9 (23.3)	N=101 14.6 (29.2)
95% CI	11.9, 16.5	8.5, 14.9
LS Mean Difference (95% CI)	2.5 (-1.4, 6.4)	
P-value	0.210	

Analysis Method	Oteseconazole N=218 n (%)	Placebo N=108 n (%)
SF-36 Total Score		
Screening	N=199	N=100
Mean (SD)	74.8 (18.3)	70.3 (23.0)
Week 48	N=197	N=101
Mean (SD)	87.2 (12.8)	84.9 (15.2)
Change from Screening	N=194	N=101
LS Mean (SE)	12.5 (21.8)	14.1 (26.4)
95% CI	11.8, 15.6	8.8, 14.1
LS Mean Difference (95% CI)	2.2 (-1.1, 5.6)	
P-value	0.186	

Source: Adapted from Table 14.2.2.4.1 and Table 14.2.2.5.1 and confirmed by reviewer using ADQS dataset
Abbreviations: ITT, intent to treat; LS, least squares; MCS, mental component score; SE, standard error; SF-36, 36 item short form survey.

16.3. Additional Analyses for Study CL-017

Applicant's Original Analysis of Primary Endpoint

As stated in the protocol, the primary efficacy outcome measure was the proportion of subjects with 1 or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT Population, which included the subjects who failed clearing their infection during the Induction Phase. Rather than considering all subjects who failed clearing their infection during the Induction Phase as having an event, as intended, the Applicant interpreted this as including such subject in the ITT population but only considered them an event if they met the definition of culture-verified acute VVC at Day 14. Only 2 of the 10 oteseconazole Induction failures and 2 of the 3 fluconazole Induction failures had a culture confirmed acute VVC episode at Day 14 and were considered as having a recurrence in the Applicant's original analysis. Since Induction Failures did not continue to the Maintenance Phase, the remaining subjects by default had missing data for the remainder of the study. Therefore, Applicant's misinterpretation of the intended primary endpoint impacted the analysis using MI for handling missing data but not the analysis where missing data were considered failures. [Table 158](#) presents the results using MI for handling missing data as reported in the CL-017 Clinical Study Report.

Table 158. Applicant's Original Analysis of Proportion of Subjects Who Had ≥1 Culture-Verified Acute VVC Episodes During Post- Randomization Through Week 50 for Trial CL-017: ITT Population

Analysis	Oteseconazole N=147	Fluconazole/Placebo N=72
Known recurrence through Week 50 (n)	6	26
Incomplete follow-up (n)	38	14
Analysis method		
Multiple imputation (average %) ^[1]	5.1	42.2
Min, max (%)	4.1, 6.8	40.3, 45.8
P-value ^[2]	<0.001	

Source: Adapted from Table 14.2.1.1 of CL-017 Study Report and confirmed by reviewer using ADEFF dataset

^[1] Missing values were imputed with multiple imputation method

^[2] Chi-square test comparing active treatment to placebo

Abbreviations: ITT, intent to treat.

Subgroup Analyses of the Primary Endpoint for Study CL-017

The subgroup analyses results for the primary endpoint based on the MI method and missing counted as failures method are summarized in [Table 159](#). The proportion of subjects with ≥ 1 culture-verified acute VVC episode during the post-randomization through Week 50 by age group, race, ethnicity, Day 14 signs and symptoms score (0, 1, and 2), and number of historic VVC episodes were lower in oteseconazole as compared to placebo.

Table 159. Subgroup Analysis of Primary Endpoint of Proportion of Subjects Who Failed Induction or Who Had ≥ 1 Culture-Verified Acute VVC Episodes During Post- Randomization Through Week 50 for Trial CL-017: ITT Population

Subgroup	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)	P-value
Age group			
18-33 Years	N=72	N=30	
Average % (MI) ^a	7.2	47.3	<0.001
No. recurrence (%) ^b	20 (27.8)	18 (60.0)	0.002
≥ 34 years	N=74	N=41	
Average % (MI)	13.4	40.7	0.002
No. recurrence (%)	24 (32.4)	22 (53.7)	0.026
Race			
White	N=88	N=42	
Average % (MI) ^a	6.3	41.2	<0.001
No. recurrence (%) ^b	26 (29.6)	21 (50.0)	0.023
Black or African American	N=47	N=27	
Average % (MI) ^a	18.3	50.4	<0.001
No. recurrence (%) ^b	16 (34.0)	19 (70.4)	0.003
Other	N=12	N=3	
Average % (MI) ^a	8.3	0	NE
No. recurrence (%) ^b	2 (16.7)	0	0.448
Ethnicity			
Hispanic or Latino	N=38	N=19	
Average % (MI) ^a	5.8	28.9	0.019
No. recurrence (%) ^b	11 (29.0)	7 (36.8)	0.546
Not Hispanic or Latino	N=109	N=53	
Average % (MI) ^a	11.8	47.9	<0.001
No. recurrence	33 (30.3)	33 (62.3)	<0.001
Day 14 Signs and Symptom Score			
0	N=63	N=25	
Average % (MI) ^a	3.8	52.8	<0.001
No. recurrence (%) ^b	16 (25.4)	14 (56.0)	0.006
1	N=37	N=22	
Average % (MI) ^a	6.2	32.7	0.021
No. recurrence (%) ^b	9 (24.3)	11 (50.0)	0.044
2	N=33	N=18	
Average % (MI) ^a	1.2	35.0	0.022
No. recurrence (%) ^b	5 (15.2)	8 (44.4)	<0.001

Subgroup	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)	P-value
Number of historic VVC episode			
0-3	N=69	N=34	
Average % (MI) ^a	11.0	31.5	0.034
No. recurrence (%) ^b	22 (31.9)	16 (47.1)	0.133
≥ 4	N=78	N=38	
Average % (MI) ^a	9.6	53.2	<0.001
No. recurrence (%) ^b	22 (28.2)	24 (63.2)	<0.001

Source: Adapted from Table 14.2.1.6 of response dated 11/23/21 for Average % (MI) and Clinical Study Report for No Recurrence (%)

[a] Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

[b]. Subjects with incomplete follow-up had their missing values imputed as failures.

The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Abbreviations: ITT, intent to treat; NE, not examined; MI, multiple imputations; VVC, vulvovaginal candidiasis.

Analyses of Selected Secondary Endpoints for Study CL-017

The results for the proportion of subjects with at least one culture-verified acute VVC infections signs and symptoms score of ≥ 3 during the Maintenance Phase (post Day 14 through Week 50) based on ITT population are summarized in [Table 160](#). The average percentage of subject with at least one culture-verified acute VVC infections during the Maintenance Phase was 3.8 % in oteseconazole and 41.1% in fluconazole/placebo using the multiple imputation method. The analysis method for missing counted as failures, 30 oteseconazole (22.6%) subjects and 33 placebo (50.8%) subjects had at least one culture-verified acute VVC infections signs and symptoms score of ≥ 3 during the Maintenance Phase. The proportion of subjects with at least one culture-verified acute VVC infections signs and symptoms score of ≥ 3 during the Maintenance Phase was statistically significantly lower in oteseconazole than fluconazole/placebo.

Table 160. Proportion of Subjects With ≥ 1 Culture-Verified Acute VVC Episode During Maintenance Phase (Post Day 14 Through Week 50) for Trial CL-017: ITT Population

Analysis Method	Oteseconazole N=147	Fluconazole/Placebo N=72
MI (average %) *	3.8	41.1
Min, max	3.0, 6.0	38.5, 44.6
P-value	<0.001	
Missing as failures**	30 (22.6)	33 (50.8)
P-value	<0.001	

Source: Adapted from Table 14.2.2.2.1 and Table 14.2.2.2.5 of and confirmed by reviewer using ADEFF dataset

*: Missing values were imputed with multiple imputation method

**: Missing values were counted as failures

#: Chi-square test comparing active treatment to place

Abbreviations: ITT, intent to treat; MI, multiple imputations; VVC, vulvovaginal candidiasis.

The results for the proportion of subjects with at least one positive culture for *Candida* species during the Maintenance Phase (post-Day 14 through Week 50) for the ITT Population are summarized in [Table 161](#). Oteseconazole was demonstrated to be superior to fluconazole/placebo in the proportion of subjects with at least one positive culture for *Candida* species during the Maintenance Phase (post-Day 14 through Week 50) using both methods for handling missing data. The average percentage of subjects with at least one positive culture for *Candida* species during the Maintenance Phase (post-Day 14 through Week 50) was 23.6% in oteseconazole and 79.7% in fluconazole/placebo using the MI method. These values are much

higher than those observed for the endpoint of ≥ 1 culture-verified acute VVC episode during the Maintenance Phase (previous [Table 160](#)) indicating many asymptomatic subjects had a positive culture.

Table 161. Proportion of Subjects With Positive Culture for *Candida* Species During the Maintenance Phase (Post Day 14 Through Week 50) for Trial CL-017: ITT Population

Analysis Method	Oteseconazole	Fluconazole/Placebo
	N=147	N=72
MI (average %) ¹	23.6	79.7
Min, max	21.1, 27.1	76.9, 84.6
P-value	<0.001	
Missing as Failures ²	52 (35.4)	51 (70.8)
P-value ³	<0.001	

Source: Adapted from Table 14.2.2.4.1 and Table 14.2.2.4.5 of and confirmed by reviewer using ADEFF dataset

¹: Missing values were imputed with multiple imputation method

²: Missing values were counted as failures

³: Chi-square test comparing active treatment to place

Abbreviations: ITT, intent to treat; MI, multiple imputations.

By Day 14, 81.3% of all subjects had a negative culture for *Candida* and 12.3% had a positive culture for *Candida*. *C. albicans* (5.9%) and *C. glabrata* (5.0%) were the most commonly reported pathogens. Mean and median signs and symptom scores in both treatment arms, at Day 14, were 1.2 and 1.0, respectively. Correspondingly, 90.4% of all subjects in the ITT population had a signs and symptoms score between 0 and 2 by Day 14 which was necessary for the subject to continue on to the maintenance phase.

Table 162. Trial CL-017 Day 14 Signs and Symptoms and Microbiologic Characteristics, ITT Population

Characteristic	Oteseconazole	Fluconazole/ Placebo	Total (N=219)
	(N=147)	(N=72)	
Day 14 culture results			
Negative for <i>Candida</i>	123 (83.7)	55 (76.4)	178 (81.3)
Positive for <i>Candida</i>	17 (11.6)	10 (13.9)	27 (12.3)
Missing/unknown	7 (4.8)	7 (9.7)	14 (6.4)
Day 14 pathogen			
<i>Candida albicans</i>	8 (5.4)	4 (5.6)	12 (5.5)
<i>Candida glabrata</i>	6 (4.1)	4 (5.6)	10 (4.6)
<i>Candida albicans, Candida glabrata</i>	1 (0.7)	0	1 (0.5)
<i>Candida krusei</i>	1 (0.7)	0	1 (0.5)
<i>Candida parapsilosis</i>	1 (0.7)	1 (1.4)	2 (0.9)
<i>Candida tropicalis</i>	0	1 (1.4)	1 (0.5)
<i>Trichosporon inkin</i>	0	1 (1.4)	1 (0.5)
Day 14 signs and symptoms score			
Mean (SD)	1.2 (1.93)	1.1 (1.37)	1.2 (1.77)
Median (min, max)	1.0 (0, 15)	1.0 (0, 9)	1.0 (0, 15)

Day 14 signs and symptoms score, by category			
0-2	133 (90.5)	65 (90.3)	198 (90.4)
3	2 (1.4)	1 (1.4)	3 (1.4)
4-8	5 (3.4)	1 (1.4)	6 (2.7)
≥9	3 (2.0)	1 (1.4)	4 (1.8)
Missing/unknown	4 (2.7)	4 (5.6)	8 (3.7)

Source: OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: ITTFL = 'Y'.

Baseline (Day 1) Pathogen - Dataset: Demographics; Filter: None.

Baseline (Day 1) Signs and Symptoms Score - Dataset: Demographics; Filter: None.

Baseline (Day 1) Signs and Symptoms Signs, by Category - Dataset: Demographics; Filter: None.

Baseline (Day 1) Potassium Hydroxide (KOH) Smear - Dataset: Demographics; Filter: None.

Baseline (Day 1) Culture Result - Dataset: Demographics; Filter: None.

Day 14 Pathogen - Dataset: Demographics; Filter: None.

Day 14 Signs and Symptoms Score - Dataset: Demographics; Filter: None.

Day 14 Signs and Symptoms Score, by Category - Dataset: Demographics; Filter: None.

Day 14 Culture Results - Dataset: Demographics; Filter: None.

Note: *Lodderomyces elongisporus* is a member of *C. parapsilosis* complex and an uncommon cause of candidemia found most often in the immunocompromised.

Abbreviations: ITT, intent to treat; SD, standard deviation

16.4. Additional Analyses for Studies CL-011, CL-012 and CL-017

Timing of Recurrence – During Maintenance Phase or Off-Treatment Follow-Up

The three efficacy studies included a treatment period of the initial episode of VVC, a maintenance phase consisting of 12 weeks of treatment, and an extended follow-up period. Determining when recurrences occur is important to understand if oteseconazole reduces recurrences only during the maintenance period or if the effect of oteseconazole continues during the off-treatment follow-up phase.

The time to recurrence during the study periods are summarized in the following tables for the three trials. Note that the largest number of recurrences on placebo occurred during the first 12 weeks of follow-up (while oteseconazole subjects were receiving the maintenance regimen). The percentages of recurrences on the oteseconazole arms were similar across the different 12-week time frames.

Table 163. Summary of Recurrences for Trials CL-011 and CL-012

Recurrence	CL-011		CL-012	
	Oteseconazole (N=217) n (%)	Placebo (N=109) n (%)	Oteseconazole (N=218) n (%)	Placebo (N=108) n (%)
No. of Recurrence	14 (6.6)	45 (42.4)	8 (3.7)	39 (36.1)
By Week 12	4 (1.8)	26 (23.9)	4 (1.8)	28 (25.9)
Week 12-24	3 (1.4)	14 (12.8)	2 (0.9)	5 (4.6)
Week 24-36	4 (1.8)	4 (3.7)	1 (0.5)	3 (2.8)
Week 36-48	3 (1.4)	1 (0.9)	1 (0.5)	3 (2.8)
Mean recurrence week	45.7	27.8	47.3	33.3

Source: Reviewer conducted analysis using ADTTE dataset

Table 164. Summary of Recurrences for Trial CL-017

Recurrence	CL-017	
	Oteseconazole (N=147) n (%)	Fluconazole/Placebo (N=72) n (%)
No. of Recurrences	4 (2.7)	24 (33.3)
At Day 14	1 (1.4)	0
By Week 12	2 (1.4)	11 (15.3)
Week 12-24	1 (1.4)	7 (9.7)
Week 24-36	0	2 (2.8)
Week 36-50	0	4 (5.6)
Mean recurrence week	36.5	35.3

Source: Reviewer conducted analysis using ADTTE dataset

There does not appear to be an increase in the number of recurrences occurring in the oteseconazole arm after treatment was stopped.

Incomplete Follow-Up

The numbers of subjects with incomplete follow-up and no known event (i.e., recurrence or not resolved) is summarized in [Table 165](#). Incomplete follow-up appears higher in the oteseconazole arm compared to the placebo arm. Though this might be partly due to the imbalance in the number of subjects in the risk set, since those subjects who already had an event and then discontinued the trial are not considered to have had missing data since they had reached the primary endpoint. To address this, we also present the percent of subject with incomplete follow-up out of those without known recurrence.

Table 165. Incomplete Follow-Up in Trials CL-011, CL-012 and CL-017

Study	Oteseconazole	Placebo
CL-011		
Subjects with incomplete follow-up	42	11
% of total	19.4% of 217	10.1% of 109
% of those without known recurrence	20.7% of 203	17.2% of 64
CL-012		
Subjects with incomplete follow-up	38	13
% of total	17.4% of 218	12.0% of 108
% of those without known recurrence	18.1% of 210	18.8% of 69
CL-017		
	Oteseconazole	Fluconazole/Placebo
Subjects with incomplete follow-up	30	13
% of total	20.4% of 147	18.1% of 72
% of those without known event (not resolved or recurrence)	22.6% of 133	28.9% of 45

Source: Reviewer conducted analysis using ADEFF datasets

Accidental Unblinding in Studies CL-011 and CL-012

Due to an error in the Interactive Response Technology system, automated emails disclosing unblinded randomization details were initially sent to the site user performing randomization in studies CL-011 and CL-012. The error in the Interactive Response Technology system was active from the start of these two studies until corrected on November 28, 2018 after which site personnel randomizing subjects no longer received the unblinded email. Unblinded emails were sent to 17 different users from 16 sites and involved the first 24 subjects of studies CL-011 (14

subjects) and CL-012 (10 subjects). This issue did not impact CL-017, which was initiated in 2019.

The Applicant was notified of this error by the contractor, (b) (4) on November 29, 2018. On the same day, the Applicant requested that the Clinical Lead (b) (4) or assigned clinical research associate contact the affected sites to investigate a) site awareness of the unblinded communication, b) if any potential dissemination of the information to other site staff or clinical research associates had occurred, c) and what actions were taken by site staff who received the unblinding email. Additionally, the Applicant sent a Note To File to the Principal Investigators on January 16, 2019 regarding the unblinding and requesting each sign a statement confirming adherence to good clinical practices (GCPs) and retrain staff on GCP particularly unblinding procedures.

The impacted sites and subjects were the following:

- Study CL-011:
 - Site 102- Subjects (b) (6)
 - Site 103- Subject (b) (6)
 - Site 105- Subjects (b) (6)
 - Site 107- Subject (b) (6)
 - Site 108- Subject (b) (6)
 - Site 114- Subject (b) (6)
 - Site 132- Subject (b) (6)
 - Site 136- Subjects (b) (6)
 - Site 147- Subjects (b) (6)
- Study CL-012:
 - Site 204- Subject (b) (6)
 - Site 215- Subject (b) (6)
 - Site 218- Subject (b) (6)
 - Site 229- Subject (b) (6)
 - Site 233- Subject (b) (6)
 - Site 240- Subjects (b) (6)
 - Site 244- Subject (b) (6)
 - Site 245- Subject (b) (6)

The Applicant removed all 24 subjects where accidental unblinding emails were sent to the site from the per-protocol population. However, they included 21 of the 24 subjects in the ITT population since none of the subjects were notified of treatment assignment and the study coordinators who received the unblinded email did not perform vaginal exams nor evaluate VVC signs and symptoms (with possibly the exception of site 136). The 3 subjects removed were from site 240 which had other GCP noncompliance issues and was removed from all analyses.

Since the ITT population is the primary analysis population, sensitivity analyses on the primary endpoint excluding the subjects with accidental unblinding as well as all subjects at the sites where unblinded emails were received were conducted to determine the robustness of the overall results based on the missing=recurrence. In CL-011, accidental unblinding occurred for 9 oteseconazole subjects (3 had recurrence, 2 had incomplete follow-up but no known recurrence, and 4 did not have a recurrence) and 4 placebo subjects (4 had recurrence and 1 did not have a

recurrence). In Study CL-012, 4 oteseconazole subjects (1 had recurrence and 3 did not have a recurrence) and 3 placebo subjects (1 each had recurrence, incomplete follow-up but no known recurrence, and no recurrence) in the ITT population had accidental unblinding. The results of these sensitivity analysis are summarized in [Table 166](#) and are robust to excluding the subjects/sites with accidental unblinding.

Table 166. Sensitivity Analysis of Culture Verified Acute VVC Episode Excluding Subjects/Sites with Accidental Unblinding in Trials CL-011 and CL012

Characteristic	CL-011		CL-012	
	Oteseconazole n (%)	Placebo n (%)	Oteseconazole n (%)	Placebo n (%)
Overall ITT	56/217 (25.8)	56/109 (51.4)	46/218 (21.0)	52/108 (48.2)
Excluding subjects with unblinding	51/208 (24.5)	52/104 (50.0)	45/214 (21.0)	50/105 (47.6)
Excluding sites with unblinding	38/173 (22.0)	44/87 (50.6)	37/192 (19.3)	43/95 (45.3)

Source: Reviewer conducted analyses using ADEFF datasets

Missing = Recurrence

Abbreviations: ITT, intent to treat; VVC, vulvovaginal candidiasis.

16.5. Trial CL-006 Trial Design

Trial CL-006 was a Phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel group, dose ranging study evaluating the safety and efficacy of oteseconazole at two different doses (150 mg and 300 mg) and at two different dosing durations (12 weeks and 24 weeks). Females were recruited from 38 clinical sites within the United States.

The trial consisted of a 1-week open-label Induction Phase where eligible, consenting participants aged ≥ 18 to <65 years old with: (a) an acute VVC infection, (b) a history of at least 3 or more acute episodes of symptomatic VVC within a 12-month period, and (c) a composite vulvovaginal signs and symptoms score of ≥ 3 received treatment with three sequential doses of fluconazole 150 mg administered every 72 hours. Fourteen days after the initial dose of fluconazole was administered, all females with a composite vulvovaginal signs and symptoms score of < 3 were randomized in a 1:1:1:1:1 fashion into the Maintenance Phase and were assigned to one of five treatment groups:

- VT-1161 low-dose (150 mg) for 12 weeks, then placebo for 12 weeks
- VT-1161 low-dose (150 mg) for 24 weeks
- VT-1161 high-dose (300 mg) for 12 weeks, then placebo for 12 weeks
- VT-1161 high-dose (300 mg) for 24 weeks
- Placebo (administered to match the VT-1161 treatment groups)

During the Maintenance Phase, participants, who were blinded to treatment as were the study investigator and the study and clinical staff, received low dose oteseconazole (150 mg + placebo) or high-dose oteseconazole daily (300 mg) for Days 1 (Baseline) through 7. Afterwards, participants received once weekly oteseconazole for either Weeks 2-12, if the participant was randomly assigned to 12-weeks of treatment or from Weeks 2-24, if the participant was randomly assigned to 24-weeks (6-month) of treatment.

Females eligible for study participation were generally healthy, non-pregnant, nonlactating females between the ages of ≥ 18 and <65 years old who were diagnosed with symptomatic acute VVC; had a history of RVVC—3 or more symptomatic episodes of acute VVC in the past 12 months, including the episode at Screening; with a signs and symptoms score of ≥ 3 at Screening

and a score of <3 at the baseline visit, and a positive potassium hydroxide wet mount. Participants were excluded if they had concomitant vulvovaginitis from other infectious pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*). Females of childbearing potential were required to use one of several acceptable birth control methods throughout the study. Full eligibility criteria can be found in the Appendix.

Study visits included: a Screening visit, randomization on Day 1 (Baseline), with follow-up clinic visits on Day 7 (± 2 days), Week 4 (± 4 days), Week 8 (± 4 days), Week 12 (± 7 days), Week 18 (± 7 days), Week 24 (± 14 days), Week 36 (± 14 days), and Week 48 (± 14 days) in which efficacy, safety, laboratory, and PK assessments were conducted. Each subject was anticipated to remain in the study for approximately 50-weeks. The primary efficacy endpoint was the proportion of subjects with 1 or more culture-verified acute VVC episodes during the Maintenance Phase through Week 48 of the study and was analyzed in the ITT population -- the primary analysis population.

Key secondary efficacy endpoints included the:

- Proportion of subjects with culture-verified acute VVC infection through Week 24 of the study
- Proportion of subjects with culture-verified acute VVC infection by pathogen
- Time to first recurrence of culture-verified acute VVC infection;

The safety and tolerability of the four dosing regimens were evaluated as key secondary objectives. Safety analyses included the assessment of AEs, clinical laboratory evaluations, vital signs and physical examinations, and 12-lead ECGs.

A total of 254 subjects enrolled in the Induction Phase of CL-006 and 215 subjects were randomly assigned to the Maintenance Phase.

CL-006 Baseline Demographic and Clinical and Microbiologic Characteristics, ITT Population

Trial CL-006 was conducted solely in the United States. A total of 215 subjects comprised the ITT population with near equal numbers of subjects randomized to each treatment arm. Key baseline demographic characteristics in the ITT population are summarized in [Table 167](#). No significant imbalances were observed across treatment groups. Mean (SD) and median age across all treatment arms were 34.6 (9.95) and 33.0, respectively. Conversely, the majority of subjects were in the 25-34 age cohort (37.2%) followed by the 35-44 age cohort (25.1%). There were no subjects in the <18 year old cohort or in the ≥ 65 year old cohorts. Over 50% of subjects were White and non-Latino, followed by Black/African-American, non-Latino subjects as seen across all treatment arms. Altogether, Latino subjects accounted for nearly 20% (18.6%) of the total ITT population. Subjects' mean (SD) and median BMIs were 27.3 and 25.6

Most subjects had 3 acute VVC episodes in the preceding 12 months (43.3%) prior to enrollment, closely followed by 4-6 acute VVC episodes in the preceding 12 months (39.5%). However, subjects in the oteseconazole 150-mg x 12 weeks arm had a higher percentage of subjects with 4-6 and 7-9 acute VVC episodes in the preceding 12 months when compared to their counterparts in the 3 other arms. Mean (SD) and median numbers of acute VVC episodes in the preceding 12 months for the entire ITT population were 4.5 (2.6) and 4.0, respectively.

Table 167. Trial CL-006 Baseline Demographic Characteristics, ITT Population

Demographics	Oteseconazole 150 mg x 12 Wks (N=42)	Oteseconazole 150 mg x 24 Wks (N=43)	Oteseconazole 300 mg x 12 Wks (N=43)	Oteseconazole 300 mg x 24 Wks (N=41)	Placebo (N=46)	Total (N=215)
Sex	42 (100.0)	43 (100.0)	43 (100.0)	41 (100.0)	46 (100.0)	215 (100.0)
Age						
Mean (SD)	35.0 (10.20)	34.6 (9.09)	34.2 (9.28)	33.8 (10.13)	35.4 (11.20)	34.6 (9.95)
Median (min, max)	33.5 (21, 58)	35.0 (22, 53)	33.0 (19, 58)	32.0 (18, 53)	33.0 (20, 60)	33.0 (18, 60)
Age, by category						
18-24	8 (19.0)	6 (14.0)	7 (16.3)	8 (19.5)	7 (15.2)	36 (16.7)
25-34	15 (35.7)	15 (34.9)	16 (37.2)	16 (39.0)	18 (39.1)	80 (37.2)
35-44	8 (19.0)	14 (32.6)	13 (30.2)	8 (19.5)	11 (23.9)	54 (25.1)
45-64	11 (26.2)	8 (18.6)	7 (16.3)	9 (22.0)	10 (21.7)	45 (20.9)
Race						
White	22 (52.4)	26 (60.5)	26 (60.5)	22 (53.7)	23 (50.0)	119 (55.3)
Black/African-American	19 (45.2)	15 (34.9)	14 (32.6)	19 (46.3)	20 (43.5)	87 (40.5)
Asian	1 (2.4)	2 (4.7)	1 (2.3)	0 (0.0)	2 (4.3)	6 (2.8)
Other	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	1 (2.2)	3 (1.4)
Ethnicity						
Non-Hispanic/Latino	35 (83.3)	33 (76.7)	35 (81.4)	37 (90.2)	35 (76.1)	175 (81.4)
Black/African-American	19 (45.2)	14 (32.6)	13 (30.2)	19 (46.3)	20 (43.5)	85 (39.5)
White	15 (35.7)	17 (39.5)	20 (46.5)	18 (43.9)	14 (30.4)	84 (39.1)
Asian	1 (2.4)	2 (4.7)	1 (2.3)	0 (0.0)	1 (2.2)	5 (2.3)
Other	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.5)
Hispanic/Latino	7 (16.7)	10 (23.3)	8 (18.6)	4 (9.8)	11 (23.9)	40 (18.6)
White	7 (16.7)	9 (20.9)	6 (14.0)	4 (9.8)	9 (19.6)	35 (16.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
Black/African-American	0 (0.0)	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	2 (0.9)
Other	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (2.2)	2 (0.9)
BMI (kg/m ²)						
Mean (SD)	27.6 (7.09)	27.4 (6.32)	26.8 (6.38)	26.7 (6.83)	27.9 (6.87)	27.3 (6.66)
Median (min, max)	24.9 (17.5, 44.1)	26.5 (18.5, 47.6)	25.4 (17.4, 46.3)	25.0 (17.2, 44.7)	26.8 (15.2, 49.6)	25.6 (15.2, 49.6)
BMI, by category						
<18.5	1 (2.4)	0 (0.0)	1 (2.3)	2 (4.9)	2 (4.3)	6 (2.8)
18.5-24.99	20 (47.6)	18 (41.9)	20 (46.5)	18 (43.9)	15 (32.6)	91 (42.3)
25-29.99	10 (23.8)	13 (30.2)	12 (27.9)	13 (31.7)	15 (32.6)	63 (29.3)
30.0-39.99	7 (16.7)	8 (18.6)	8 (18.6)	5 (12.2)	12 (26.1)	40 (18.6)
≥40	4 (9.5)	3 (7.0)	2 (4.7)	3 (7.3)	2 (4.3)	14 (6.5)
Missing	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Demographics	Oteseconazole 150 mg x 12 Wks (N=42)	Oteseconazole 150 mg x 24 Wks (N=43)	Oteseconazole 300 mg x 12 Wks (N=43)	Oteseconazole 300 mg x 24 Wks (N=41)	Placebo (N=46)	Total (N=215)
Region/Country						
USA	42 (100.0)	43 (100.0)	43 (100.0)	41 (100.0)	46 (100.0)	215 (100.0)
South	20 (47.6)	21 (48.8)	18 (41.9)	19 (46.3)	25 (54.3)	103 (47.9)
West	11 (26.2)	10 (23.3)	13 (30.2)	11 (26.8)	11 (23.9)	56 (26.0)
Northeast	10 (23.8)	10 (23.3)	11 (25.6)	10 (24.4)	8 (17.4)	49 (22.8)
Midwest	1 (2.4)	2 (4.7)	1 (2.3)	1 (2.4)	2 (4.3)	7 (3.3)
No. of acute VVC in prior 12 months						
Mean (SD)	4.6 (2.04)	4.8 (2.85)	4.7 (2.49)	4.7 (2.54)	5.2 (2.90)	4.8 (2.57)
Median (min, max)	4.0 (3, 12)	4.0 (3, 12)	4.0 (3, 13)	4.0 (3, 16)	4.0 (3, 13)	4.0 (3, 16)
No. of acute VVC in prior 12 months, by category						
3	17 (40.5)	21 (48.8)	19 (44.2)	17 (41.5)	19 (41.3)	93 (43.3)
4-6	19 (45.2)	14 (32.6)	17 (39.5)	18 (43.9)	17 (37.0)	85 (39.5)
7-9	5 (11.9)	1 (2.3)	4 (9.3)	4 (9.8)	5 (10.9)	19 (8.8)
≥10	1 (2.4)	7 (16.3)	3 (7.0)	2 (4.9)	5 (10.9)	18 (8.4)
Pathogen at baseline						
Missing/Unknown/No growth	39 (92.9)	31 (72.1)	36 (83.7)	39 (95.1)	44 (95.7)	189 (87.9)
<i>Candida albicans</i>	2 (4.8)	11 (25.6)	5 (11.6)	1 (2.4)	1 (2.2)	20 (9.3)
<i>Candida glabrata</i>	1 (2.4)	0 (0.0)	1 (2.3)	1 (2.4)	0 (0.0)	3 (1.4)
<i>Candida albicans</i> , <i>Candida glabrata</i>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.2)	1 (0.5)
<i>Candida lusitaniae</i>	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.5)
<i>Candida tropicalis</i>	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

NDA 215888
Vivjoa (oteseconazole)

Demographics	Oteseconazole 150 mg x 12 Wks (N=42)	Oteseconazole 150 mg x 24 Wks (N=43)	Oteseconazole 300 mg x 12 Wks (N=43)	Oteseconazole 300 mg x 24 Wks (N=41)	Placebo (N=46)	Total (N=215)
Signs and symptoms score at baseline						
Mean (SD)	0.7 (0.82)	0.6 (0.76)	0.6 (0.73)	0.4 (0.71)	0.5 (0.72)	0.6 (0.75)
Median (Min, Max)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)

Source: OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: ITTFL = 'Y'.

Sex - Dataset: Demographics; Filter: None.

Age - Dataset: Demographics; Filter: None.

Age, by Category - Dataset: Demographics; Filter: None.

Race - Dataset: Demographics; Filter: None.

Ethnicity - Dataset: Demographics; Filter: None.

BMI (kg/m2) - Dataset: Demographics; Filter: None.

BMI, by Category - Dataset: Demographics; Filter: None.

Region/Country - Dataset: Demographics; Filter: None.

No. of Acute VVC in Prior 12 Months - Dataset: Demographics; Filter: None.

No. of Acute VVC in Prior 12 Months, by Category - Dataset: Demographics; Filter: None.

Pathogen at Baseline - Dataset: Demographics; Filter: None.

Signs and Symptoms Score at Baseline - Dataset: Demographics; Filter: None.

SD = Standard Deviation.

Abbreviations: BMI, body mass index; ITT, intent to treat; SD, standard deviation; VVC, vulvovaginal candidiasis; wk, week

CL-006 Efficacy Results

Primary Efficacy Endpoint

The proportion of subjects with 1 or more culture-verified acute VVC infections through Week 48 for the ITT population was lower in the VT-1161 treatment groups (2 [4.8%] subjects in the 150 mg 12 weeks group, 3 [7.0%] subjects in the 150 mg 24 weeks group, 0 [0.0%] subjects in the 300 mg 12 weeks group, and 2 [4.9%] subjects in the 300 mg 24 weeks group) compared with the placebo group (24 [52.2%] subjects). The differences were statistically significant in each of the VT-1161 treatment groups compared with placebo ($p < 0.0001$) ([Table 168](#)). The results observed in the mITT, mITT2, mITT3, and PP populations were similar to those recorded in the ITT population.

The results of sensitivity analyses, subgroup analyses, and exploratory analyses were similar to the primary analysis findings.

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Table 168. Percentage of Subjects With 1 or More Culture-Verified Acute VVC Infections Through Week 48 (Intent-to-Treat Population)

Table 2-1 Percentage of Subjects with 1 or More Culture-Verified Acute VVC Infections through Week 48 (Intent-to-Treat Population)

		VT-1161				
Culture-Verified Acute VVC Infection		150 mg 12 Weeks (N=42)	150 mg 24 Weeks (N=43)	300 mg 12 Weeks (N=43)	300 mg 24 Weeks (N=41)	Placebo (N=46)
	Yes	n (%)	2 (4.8%)	3 (7.0%)	0	2 (4.9%)
	95% CI	(0.6%, 16.2%)	(1.5%, 19.1%)	(0.0%, 8.2%)	(0.6%, 16.5%)	(36.9%, 67.1%)
	Odds Ratio ^a	0.0308	0.0414	0.0000	0.0438	
	95% CI ^a	(0.0056, 0.1695)	(0.0088, 0.1944)	(N/A, N/A)	(0.0087, 0.2210)	
	P-value ^a	<0.0001	<0.0001	<0.0001	<0.0001	

Abbreviations: N/A, not applicable; VVC, vulvovaginal candidiasis.

Note: Culture-verified acute vulvovaginal candidiasis (VVC) infection was defined as a positive fungal culture for *Candida* species associated with clinical signs and symptoms score ≥ 3 . Percentage calculations assumed that subjects who discontinued the study prior to a culture-verified VVC episode (censored subjects) had no episodes. The 95% CIs for the proportion of subjects with 1 or more culture-verified acute VVC infections through Week 48 were calculated using an exact method (Clopper-Pearson).

^a Odds ratio, corresponding 95% CIs and p-values were from Cochran-Mantel-Haenszel tests comparing each VT-1161 treatment group to placebo stratified by site.

Source: Table 2-1 of CL-006 Clinical Study Report

17. Clinical Safety: Additional Information and Assessment

Trials CL-011, CL-012, and CL-017

Table 169. Baseline Demographic and Clinical Characteristics, Safety Population (Pooled Phase 3 Trials-CL-011, CL-012, CL-017)

Variable	Oteseconazole 1050 mg/150 mg 11 Weeks (N=580)	Placebo (N=291)	Total (N=871)
Sex			
Female	580 (100.0)	291 (100.0)	871 (100.0)
Age			
Mean (SD)	34.3 (10.08)	35.0 (10.73)	34.5 (10.30)
Median (min, max)	33.0 (16, 78)	34.0 (16, 78)	34.0 (16, 78)
Age cohort, by category			
<18	2 (0.3)	1 (0.3)	3 (0.3)
18-24	109 (18.8)	54 (18.6)	163 (18.7)
25-34	203 (35.0)	92 (31.6)	295 (33.9)
35-44	175 (30.2)	95 (32.6)	270 (31.0)
45-64	88 (15.2)	47 (16.2)	135 (15.5)
≥65	3 (0.5)	2 (0.7)	5 (0.6)
Race			
White	435 (75.0)	219 (75.3)	654 (75.1)
Black or African American	96 (16.6)	53 (18.2)	149 (17.1)
Asian	36 (6.2)	15 (5.2)	51 (5.9)
Other	10 (1.7)	3 (1.0)	13 (1.5)
American Indian or Alaska Native	2 (0.3)	1 (0.3)	3 (0.3)
Unknown	1 (0.2)	0	1 (0.1)
Ethnicity			
Not Hispanic or Latino	492 (84.8)	248 (85.2)	740 (85.0)
White	365 (62.9)	183 (62.9)	548 (62.9)
Black or African American	86 (14.8)	49 (16.8)	135 (15.5)
Asian	32 (5.5)	15 (5.2)	47 (5.4)
Other	7 (1.2)	0	7 (0.8)
American Indian or Alaska Native	2 (0.3)	1 (0.3)	3 (0.3)
Hispanic or Latino	86 (14.8)	43 (14.8)	129 (14.8)
White	70 (12.1)	36 (12.4)	106 (12.2)
Black or African American	9 (1.6)	4 (1.4)	13 (1.5)
Other	2 (0.3)	3 (1.0)	5 (0.6)
Asian	4 (0.7)	0	4 (0.5)
Unknown	1 (0.2)	0	1 (0.1)
Unknown	2 (0.3)	0	2 (0.2)
Black or African American	1 (0.2)	0	1 (0.1)
Other	1 (0.2)	0	1 (0.1)

Variable	Oteseconazole 1050 mg/150 mg 11 Weeks (N=580)	Placebo (N=291)	Total (N=871)
Region/Country			
North America	319 (55.0)	159 (54.6)	478 (54.9)
United States	311 (53.6)	151 (51.9)	462 (53.0)
Canada	8 (1.4)	8 (2.7)	16 (1.8)
Europe	229 (39.5)	120 (41.2)	349 (40.1)
Bulgaria	50 (8.6)	23 (7.9)	73 (8.4)
Czech Republic	51 (8.8)	22 (7.6)	73 (8.4)
Romania	43 (7.4)	28 (9.6)	71 (8.2)
Poland	33 (5.7)	24 (8.2)	57 (6.5)
Belgium	18 (3.1)	8 (2.7)	26 (3.0)
Ukraine	17 (2.9)	9 (3.1)	26 (3.0)
Great Britain	9 (1.6)	3 (1.0)	12 (1.4)
Hungary	8 (1.4)	3 (1.0)	11 (1.3)
Japan	32 (5.5)	12 (4.1)	44 (5.1)
Japan	32 (5.5)	12 (4.1)	44 (5.1)
BMI (kg/m²)			
Mean (SD)	25.9 (6.99)	26.3 (7.49)	26.0 (7.2)
Median (Min, Max)	23.9 (12.8, 58.6)	24.7 (16.2, 62.4)	24.0 (12.8, 62.4)
BMI category			
<18.5	32 (5.5)	15 (5.2)	47 (5.4)
18.5-24.99	307 (52.9)	136 (46.7)	443 (50.9)
25-29.99	107 (18.4)	85 (29.2)	192 (22.0)
30.00-39.99	103 (17.8)	38 (13.1)	141 (16.2)
≥40.0	31 (5.3)	17 (5.8)	48 (5.5)
Diabetes mellitus			
N	559 (96.4)	280 (96.2)	839 (96.3)
Y	21 (3.6)	11 (3.8)	32 (3.7)
No. of acute VVC episodes in the past 12 months			
Mean (SD)	4.4 (2.48)	4.4 (2.11)	4.4 (2.36)
Median (min, max)	3.0 (3, 20)	4.0 (3, 13)	4.0 (3, 20)
No. of acute VVC episodes in the past 12 months, by category			
3	297 (51.2)	138 (47.4)	435 (49.9)
4-6	216 (37.2)	119 (40.9)	335 (38.5)
7-9	28 (4.8)	17 (5.8)	45 (5.2)
≥10	39 (6.7)	17 (5.8)	56 (6.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
AGE Category - Dataset: Demographics; Filter: None.
Age - Dataset: Demographics; Filter: None.
Age Cohort, by Category - Dataset: Demographics; Filter: None.
Race - Dataset: Demographics; Filter: None.
Ethnicity - Dataset: Demographics; Filter: None.
Region/Country - Dataset: Demographics; Filter: None.
BMI (kg/m²) - Dataset: Demographics; Filter: None.
BMI Category - Dataset: Demographics; Filter: None.
Diabetes Mellitus - Dataset: Demographics; Filter: None.
No. of Acute VVC Episodes in the Past 12 Months - Dataset: Demographics; Filter: None.
No. of Acute VVC Episodes in the Past 12 Months, by Category - Dataset: Demographics; Filter: None.
Abbreviations: BMI, body mass index; SD, standard deviation; VVC, vulvovaginal candidiasis

Trial CL-006

Table 170. Treatment-Emergent Adverse Events Occurring at ≥1% Frequency in Combined Oteseconazole Treatment Group by System Organ Class and Preferred Term/Grouped Query, Safety Population, Phase 2 Trial 006 (ISS)

System Organ Class Preferred Term/Grouped Query	OTE 150 mg 12 weeks N=41 n (%)	OTE 150 mg 24 weeks N=42 n (%)	OTE 300 mg 12 weeks N=42 n (%)	OTE 300 mg 24 weeks N=41 n (%)	Combined OTE Trial 006 N=166 n (%)	PLB N=45 n (%)	Risk Difference Combined OTE vs. PLB (%) (95% CI)
Infections and infestations	16 (39.0)	21 (50.0)	22 (52.4)	19 (46.3)	78 (47.0)	29 (64.4)	-17.5 (-33.4, -1.5)
Urinary tract infections	4 (9.8)	4 (9.5)	6 (14.3)	8 (19.5)	22 (13.3)	10 (22.2)	-9.0 (-22.2, 4.2)
Bacterial vaginosis	7 (17.1)	6 (14.3)	7 (16.7)	1 (2.4)	21 (12.7)	9 (20.0)	-7.3 (-20.1, 5.4)
Nasopharyngitis/Upper respiratory tract infections	3 (7.3)	4 (9.5)	7 (16.7)	4 (9.8)	18 (10.8)	4 (8.9)	2.0 (-7.6, 11.5)
Sinusitis	5 (12.2)	8 (19.0)	3 (7.1)	2 (4.9)	18 (10.8)	3 (6.7)	4.2 (-4.5, 12.9)
Gastroenteritis	1 (2.4)	0	1 (2.4)	2 (4.9)	4 (2.4)	1 (2.2)	0.2 (-4.7, 5.1)
Influenza	0	0	3 (7.1)	1 (2.4)	4 (2.4)	0	2.4 (0.1, 4.7)
Herpes simplex infection	0	1 (2.4)	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Papilloma viral infection	1 (2.4)	0	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Pneumonia	0	0	1 (2.4)	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Trichomoniasis	1 (2.4)	0	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Vulvitis/vulvovaginitis	0	1 (2.4)	0	1 (2.4)	2 (1.2)	1 (2.2)	-1.0 (-5.6, 3.6)
Gastrointestinal disorders	9 (22.0)	10 (23.8)	6 (14.3)	3 (7.3)	28 (16.9)	5 (11.1)	5.8 (-5.0, 16.6)
Nausea	2 (4.9)	3 (7.1)	2 (4.8)	2 (4.9)	9 (5.4)	1 (2.2)	3.2 (-2.3, 8.7)
Abdominal pain	4 (9.8)	2 (4.8)	0	0	6 (3.6)	0	3.6 (0.8, 6.5)
Abdominal distension	0	3 (7.1)	2 (4.8)	0	5 (3.0)	0	3.0 (0.4, 5.6)
Diarrhea	1 (2.4)	2 (4.8)	1 (2.4)	1 (2.4)	5 (3.0)	1 (2.2)	0.8 (-4.2, 5.8)
Constipation	2 (4.9)	0	0	1 (2.4)	3 (1.8)	1 (2.2)	-0.4 (-5.2, 4.3)
Dental caries	1 (2.4)	0	1 (2.4)	0	2 (1.2)	0	1.2 (-0.5, 2.9)
Vomiting	0	1 (2.4)	1 (2.4)	0	2 (1.2)	1 (2.2)	-1.0 (-5.6, 3.6)
Reproductive system and breast disorders	9 (22.0)	7 (16.7)	7 (16.7)	4 (9.8)	27 (16.3)	10 (22.2)	-6.0 (-19.3, 7.4)
Vulvovaginal irritation	4 (9.8)	3 (7.1)	2 (4.8)	0	9 (5.4)	2 (4.4)	1.0 (-6.0, 7.9)
Menorrhagia/metrorrhagia	0	2 (4.8)	3 (7.1)	0	5 (3.0)	1 (2.2)	0.8 (-4.2, 5.8)
Vulvovaginal pruritus	2 (4.9)	1 (2.4)	2 (4.8)	0	5 (3.0)	2 (4.4)	-1.4 (-8.0, 5.1)
Vulvovaginal dryness	2 (4.9)	0	1 (2.4)	0	3 (1.8)	0	1.8 (-0.2, 3.8)
Dysmenorrhea	1 (2.4)	0	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Dyspareunia	1 (2.4)	0	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Vaginal discharge	1 (2.4)	0	0	1 (2.4)	2 (1.2)	1 (2.2)	-1.0 (-5.6, 3.6)

System Organ Class Preferred Term/Grouped Query	OTE 150 mg 12 weeks N=41 n (%)	OTE 150 mg 24 weeks N=42 n (%)	OTE 300 mg 12 weeks N=42 n (%)	OTE 300 mg 24 weeks N=41 n (%)	Combined OTE Trial 006 N=166 n (%)	PLB N=45 n (%)	Risk Difference Combined OTE vs. PLB (%) (95% CI)
Skin and subcutaneous tissue disorders	5 (12.2)	5 (11.9)	7 (16.7)	3 (7.3)	20 (12.0)	4 (8.9)	3.2 (-6.5, 12.8)
Rash	2 (4.9)	1 (2.4)	3 (7.1)	0	6 (3.6)	1 (2.2)	1.4 (-3.8, 6.6)
Acne	0	1 (2.4)	0	1 (2.4)	2 (1.2)	1 (2.2)	-1.0 (-5.6, 3.6)
Dermatitis	0	0	1 (2.4)	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Eczema	0	1 (2.4)	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Pruritus	1 (2.4)	0	1 (2.4)	0	2 (1.2)	0	1.2 (-0.5, 2.9)
Musculoskeletal and connective tissue disorders	3 (7.3)	4 (9.5)	5 (11.9)	5 (12.2)	17 (10.2)	1 (2.2)	8.0 (1.7, 14.3)
Back pain	1 (2.4)	2 (4.8)	2 (4.8)	2 (4.9)	7 (4.2)	0	4.2 (1.2, 7.3)
Arthralgia	1 (2.4)	0	3 (7.1)	2 (4.9)	6 (3.6)	0	3.6 (0.8, 6.5)
Musculoskeletal pain	0	1 (2.4)	0	2 (4.9)	3 (1.8)	0	1.8 (-0.2, 3.8)
Pain in extremity	0	2 (4.8)	0	1 (2.4)	3 (1.8)	0	1.8 (-0.2, 3.8)
Muscle spasms	0	0	1 (2.4)	1 (2.4)	2 (1.2)	1 (2.2)	-1.0 (-5.6, 3.6)
Neck pain	1 (2.4)	0	1 (2.4)	0	2 (1.2)	0	1.2 (-0.5, 2.9)
Nervous system disorders	6 (14.6)	2 (4.8)	3 (7.1)	3 (7.3)	14 (8.4)	6 (13.3)	-4.9 (-15.7, 5.9)
Headache	5 (12.2)	0	3 (7.1)	2 (4.9)	10 (6.0)	6 (13.3)	-7.3 (-17.9, 3.3)
Dizziness	0	0	1 (2.4)	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
Injury, poisoning and procedural complications	3 (7.3)	4 (9.5)	1 (2.4)	4 (9.8)	12 (7.2)	3 (6.7)	0.6 (-7.7, 8.8)
Contusion	0	2 (4.8)	0	2 (4.9)	4 (2.4)	1 (2.2)	0.2 (-4.7, 5.1)
Procedural pain	2 (4.9)	1 (2.4)	0	0	3 (1.8)	0	1.8 (-0.2, 3.8)
Limb injury	0	1 (2.4)	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)
General disorders and administration site conditions	1 (2.4)	3 (7.1)	2 (4.8)	0	6 (3.6)	1 (2.2)	1.4 (-3.8, 6.6)
Fatigue	0	2 (4.8)	1 (2.4)	0	3 (1.8)	1 (2.2)	-0.4 (-5.2, 4.3)
Renal and urinary disorders	3 (7.3)	0	1 (2.4)	2 (4.9)	6 (3.6)	0	3.6 (0.8, 6.5)
Dysuria	1 (2.4)	0	1 (2.4)	2 (4.9)	4 (2.4)	0	2.4 (0.1, 4.7)
Psychiatric disorders	1 (2.4)	1 (2.4)	2 (4.8)	1 (2.4)	5 (3.0)	0	3.0 (0.4, 5.6)
Anxiety	1 (2.4)	0	1 (2.4)	1 (2.4)	3 (1.8)	0	1.8 (-0.2, 3.8)
Depression	1 (2.4)	0	1 (2.4)	0	2 (1.2)	0	1.2 (-0.5, 2.9)

System Organ Class Preferred Term/Grouped Query	OTE 150 mg 12 weeks N=41 n (%)	OTE 150 mg 24 weeks N=42 n (%)	OTE 300 mg 12 weeks N=42 n (%)	OTE 300 mg 24 weeks N=41 n (%)	Combined OTE Trial 006 N=166 n (%)	PLB N=45 n (%)	Risk Difference Combined OTE vs. PLB (%) (95% CI)
Respiratory, thoracic and mediastinal disorders	1 (2.4)	2 (4.8)	0	1 (2.4)	4 (2.4)	0	2.4 (0.1, 4.7)
Cough	1 (2.4)	0	0	1 (2.4)	2 (1.2)	0	1.2 (-0.5, 2.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event reported on the eCRF that occurred on or after the initiation of study drug. AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

Duration is approx. 50 weeks.

The analysis included all TEAEs by GQ and PT $\geq$ 1% as found in the combined oteseconazole treatment group.

*Subjects who experienced more than one TEAE in the GQ: VMTVT1161CL006-13-059; VMTVT1161CL006-19-003; VMTVT1161CL006-19-006; VMTVT1161CL006-23-013; VMTVT1161CL006-26-007; VMTVT1161CL006-32-001; VMTVT1161CL006-33-006; VMTVT1161CL006-36-011

Abbreviations: PLB, placebo; OTE, oteseconazole.

17.1. Nonfatal Treatment-Emergent SAEs Narratives

17.1.1. Trial CL-011 Nonfatal Treatment-Emergent SAEs

CL-011 Oteseconazole Arm

Subject (b) (6) **(Oteseconazole) (PTs: Tubo-Ovarian Abscess and Endometriosis)**

A 45-year-old White, non-Latino Canadian female with a past medical history noted for asthma, fibromyalgia, pelvic pain, and six prior episodes of VVC in the past 12 months. The subject was randomized into the Maintenance Phase of the study and received the first dose of oteseconazole on Study Day 1. The subject received the last dose of oteseconazole on Study Day 84.

On Study Day 31, the subject presented to the emergency room with a complaint of persistent pelvic pain. On Study Day 38, the subject was diagnosed with a left tubo-ovarian abscess, via ultrasound, and was then hospitalized.

Key concomitant medications included: piperacillin-tazobactam (Study Days 38-40) and was later switched to oral moxifloxacin (Study Days 40-52).

On Study Day 60, the subject underwent a bilateral ovariectomy/hysterectomy for removal of the left tubo-ovarian abscess, when an endometrioma (Study Day 60) was incidentally discovered. These two SAEs (tubo-ovarian abscess; Study Days 38-60) and (endometriosis; Study Day 60) were resolved on Study Day 60. The final dose of oteseconazole was given on Study Day 84.

Study Investigator/Applicant Impression: The Study Investigator determined that neither serious adverse event (SAE) was related to either fluconazole induction or oteseconazole maintenance.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narrative and agrees that the observed SAEs were unrelated to either study treatment.

Subject (b) (6) **(Oteseconazole) (PT: Limb Traumatic Amputation)**

A 51-year-old Black/African-American, non-Latino female with a past medical history most notable for anxiety/depression, iron deficiency anemia, menorrhagia, fibroids, and s/p tubal ligation (2001). The subject had three prior episodes of acute VVC in the past 12 months. The subject was randomized into the study's Maintenance Phase and received the first dose of oteseconazole on Study Day 1 and last dose on Study Day 87.

On Study Day 334, the subject reportedly sustained a treatment-emergent SAE coded to limb traumatic amputation (Study Days 334-358) secondary to a motor vehicle accident. Following this accident, they were sent emergently to the OR for debridement. The following day the subject underwent an open reduction and internal fixation for repair of their right radial fracture and anterior tibialis tendon. The subject required several operations and afterwards was transferred to a rehab facility. This event met three SAE criteria including: being life-threatening, resulting in persistent/significant disability and requiring hospitalization due to multiple fractures, including facial fractures, and abrasions.

Study Investigator/Applicant Impression: The Study Investigator determined that the reported events traumatic amputation of leg below left knee, facial fractures and motor vehicle accident were unrelated to fluconazole or oteseconazole. The outcome of the event was categorized as ongoing.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narratives and agrees that the observed SAE was unrelated of oteseconazole exposure.

Subject (b) (6) (Oteseconazole) (PT: Postoperative Wound Infection)

A 47-year-old Black/African American, non-Latino female with a prior medical history most notable for diabetes, hypertension, osteoarthritis, gastroesophageal reflux disease (GERD), and five episodes of acute VVC in the past 12 months. The subject was randomized into the study's Maintenance Phase and received their first dose of oteseconazole on Study Day 1. They received their last dose on Study Day 25 and completed participation in the Maintenance Phase on Study Day 344.

The subject underwent a right knee replacement on Study Day 264. The post-operative course was complicated by pain, swelling, redness, and drainage at the incision site for which the subject presented at the hospital on Study Day 270 and was diagnosed with an infection (postoperative wound infection; Study Days 270-273). This occurrence was reported as a treatment-emergent SAE. The subject was discharged from hospital on Study Day 273. The outcome of the event was reported as resolved. Action taken was not applicable.

Study Investigator/Applicant Impression: The Study Investigator and Applicant assessed the event as being unrelated to fluconazole induction therapy or oteseconazole due to the lack of a temporal association between the event and receipt of the last dose of the oteseconazole (which was 8 months prior). Osteoarthritis and diabetes were predisposing factors.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narrative and agrees that the observed SAE was unrelated to oteseconazole exposure.

Trial CL-011 Placebo Arm

Subject (b) (6) (Placebo) (PT: Appendicitis)

A 25-year-old White, non-Latino Polish female with a past medical history significant for recurrent VVC, with a history of three acute VVC episodes in the prior 12 months. The subject was randomized into the study's Maintenance Phase and received the first dose of placebo on Study Day 1.

On Study Day 75, the subject developed lower abdominal pain, presented to the hospital and underwent a laparoscopic appendectomy for the treatment-emergent SAE (appendicitis; Study Days 75-78). The SAE ended on Study Day 78. The outcome of the event was reported as resolved.

Study Investigator/Applicant Impression: The Study Investigator assessed the event as being unrelated to receipt of placebo.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed all accompanying data and the case narrative and agrees that the observed SAE was not due to exposure to placebo.

Subject (b) (6) (Placebo) (PT: Vaginal Hemorrhage)

A 23-year-old White, non-Latino Polish female with a past medical history significant for diabetes mellitus, type 1 (since (b) (6)) and a history of RVVC, with five episodes of acute VVC in the previous 12 months. The subject was randomized into the study's Maintenance Phase and received the first dose of placebo on Study Day 1, and the last dose of placebo on Study Day 85.

On Study Day 133, the subject developed vaginal bleeding (vaginal hemorrhage; Study Day 133) for which they were hospitalized and subsequently found to be pregnant. The subject had reported using oral contraceptives in conjunction with condoms with spermicide as a barrier method of contraception. The outcome of the vaginal bleeding was reported as resolved on Study Day 137. The subject withdrew consent and discontinued study participation on Study Day 196. The outcome of the pregnancy was unknown since the subject refused to cooperate any further with the Applicant.

***Clinical Reviewer's Assessment:** Clinical reviewer has reviewed accompanying data and the subject narrative and cannot comment on the relationship between the reported finding to study drug exposure since the outcome of the event remained unknown.*

Subject (b) (6) (Placebo) (PTs: Bronchitis/Pneumonia/Acute Respiratory Failure, x2/Asthma, x2):

A 21-year-old Black American, non-Latino female with a past medical history significant for asthma, seasonal allergies, and a history of RVVC, with three episodes of acute VVC within the previous 12 months. The subject was randomized into the Maintenance Phase of CL-011 and received their first dose of placebo on Study Day 1. The subject received their final dose of placebo on Study Day 19, prior to the reported SAE. The subject completed study participation on Study Day 351.

On Study Day 183, three days prior to an emergency room visit, they developed shortness of breath and a persistent cough productive of thick, yellow-green sputum. The subject was admitted into the hospital the following day, Study Day 184, and diagnosed with the treatment-emergent SAEs: bronchitis (Study Days 183-185), asthma x 2 (Study Days 183-185; Study Days 327-334), and acute hypoxic respiratory failure (Study Days 183-185; Study Days 327-334), for which they received amoxicillin-clavulanic acid (Augmentin) and inhaled steroids. The subject was discharged from the hospital on Study Day 185 when both SAEs were determined to have resolved. PT asthma was assessed as being triggered by the bronchitis.

***Study Investigator/Applicant Impression:** Both the Study Investigator and the Applicant determined that due to the lack of a temporal association between the SAEs and the placebo, that the events were unrelated to the placebo. The subject's underlying medical conditions (marijuana use, asthma) were deemed risk factors for the observed SAEs.*

***Clinical Reviewer's Assessment:** Clinical reviewer has reviewed accompanying data and case narrative and agrees that the observed SAEs were unrelated to exposure to placebo.*

17.1.2. Trial CL-012 Nonfatal Treatment-Emergent SAEs

Trial CL-012 Oteseconazole Arm

Subject (b) (6) (Oteseconazole) (PT: Back Pain)

A 54-year-old White, non-Latino Belgian female with a reported past medical history of gastric hernia (since (b) (6)), menopause (since (b) (6)), s/p thyroidectomy (since (b) (6)); and three episodes of acute VVC in the previous 12 months. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1, and the final dose on Study Day 85.

On Study Day 8, the subject experienced an initial episode of back pain for which the subject took ibuprofen (Study Days 8-77). The subject discontinued ibuprofen on Study Day 77 after developing an idiosyncratic allergic reaction and was hospitalized on Study Day 129 for an elective back surgery. This treatment-emergent SAE was reported as ongoing and at the time of reporting, remained unresolved. On Study Day 337, the subject completed the study.

Study Investigator/Applicant Impression: Both the Study Investigator and the Applicant assessed the SAE, back pain, as being unrelated to the oteseconazole.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and the case narrative and agrees that the observed SAE was unrelated to oteseconazole exposure.

Subject (b) (6) (Oteseconazole) (PT: Motor Dysfunction)

A 36-year-old White, non-Latino female from the Czech Republic with a relevant past medical history of hypothyroidism (since (b) (6)), meningitis (b) (6) abdominal teratoma (b) (6) diagnostic laparoscopy (b) (6) knee surgery (b) (6) and a C-section (b) (6). In the 12 months prior to study participation, the subject had five episodes of acute VVC reported. The subject was randomized into the Maintenance Phase of the study and received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole on Study Day 87.

The subject was hospitalized on Study Day 99 for left-sided hemiparesis of unknown etiology (motor dysfunction). Computed tomography (CT) of head and magnetic resonance imaging (MRI) of brain were unremarkable. The subject's National Institutes of Health stroke scale was 4, corresponding to a minor stroke, and they were transferred to a rehabilitation center where motor function improved. The subject was discharged from the hospital on Study Day 103. The event was later updated to psychogenic motor disorder (Study Days 99 through 206). The event was listed as ongoing at the time of the narrative report.

Study Investigator/Applicant Impression: The Study Investigator and Applicant assessed the above-described event as being unrelated either to fluconazole induction or oteseconazole maintenance therapy. MRI venography brain scan was performed to rule out a transient ischemic attack. The subject's concomitant use of contraceptive medication since 2018 was deemed a potential contributing factor to this reported transient ischemic attack.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and narrative and agrees with the Study Investigator and Applicant that the observed SAE was unrelated to oteseconazole exposure.*

Subject (b) (6) **(Oteseconazole) (PT: Deep Vein Thrombosis)**

A 33-year-old White, non-Latino female from the Czech Republic with no prior past medical history aside from a history of recurrent VVC. In the 12 months prior to study participation, the subject had reported 12 acute episodes of VVC. The only pre-enrollment medication was chlormadinone acetate/ethinyl estradiol (Bellara), a hormonal contraceptive (Study Days 7 through 106). The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1, and the final dose of oteseconazole was administered on Study Day 84. On Study Day 336, the subject completed participation in the study.

On Study Day 109, the subject was hospitalized for a deep vein thrombosis (DVT) in the common iliac vein that was detected on both ultrasound and CT (Study Days 108 through 176). The subject was initially treated with:

- Unfractionated heparin (Study Days 109, 110, 109-111) and was then transitioned to the oral anticoagulant apixaban for treatment of the DVT (Study Days 113-120; Study Days 121-199)
- Tramadol (Study Days 109-113)
- Metamizole (an analgesic anti-inflammatory) (Study Days 110-113; Study Days 113-176).

No action was reportedly taken with oteseconazole following SAE since the event occurred post-oteseconazole exposure. The event was described as ongoing at the time of the narrative report.

Study Investigator's/Applicant's Impression: The Study Investigator and the Applicant determined that the SAE was unrelated either to receipt of fluconazole or oteseconazole exposure. They believed that the concomitant use of hormonal contraception was a predisposing factor in the development of DVT.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and case narrative and agrees that the observed SAE was unlikely due to oteseconazole exposure.*

Subject (b) (6) **(Oteseconazole) (PT: Uterine Polyp)**

A 42-year-old White, non-Latino Romanian female with a past medical history of thalassemia, minor; uterine fibroids s/p myomectomy (in (b) (6)) and a history of recurrent VVC. In the 12 months prior to study participation, the subject had four episodes of acute VVC. Their only pre-enrollment medication was desogestrel/ethinyl estradiol (Marvelon), a hormonal contraceptive. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1, and the final dose of oteseconazole on Study Day 84. The last dose of oteseconazole was administered prior the onset of the reported SAE was on Study Day 56. The subject completed participation in the Maintenance Phase on Study Day 337.

The subject was diagnosed, via hysteroscopy, with an endometrial polyp (uterine polyp; Study Day 58-137). On Study Day 136, the subject was hospitalized for a hysteroscopic polypectomy and received prophylactic antibiotics. The subject was discharged on Study Day 137. The SAE was reported as being resolved after the endometrial surgery.

Study Investigator's/Applicant's Impression: Neither the Study Investigator nor the Applicant assessed the uterine polyp as being related to either fluconazole or oteseconazole exposure. They noted that the subject had a history of uterine fibroma and was s/p a uterine myomectomy prior to the event.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and case narrative and agrees that the observed SAE was unrelated to oteseconazole exposure.

Subject (b) (6) (Oteseconazole) (PT: Sinusitis)

A 39-year-old White, non-Latino Romanian female with a past medical history noted for s/p exploratory laparoscopy (b) (6) and s/p bilateral tubal ligation (b) (6), in vitro fertilization (b) (6) a C-section (b) (6) and recurrent VVC. In the 12 months prior to study participation, the reported three episodes of acute VVC. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole on Study Day 86, prior to SAE onset. The subject completed participation in the study on Study Day 364.

On an unspecified date, the subject was hospitalized with a headache and "limited movements of the head," latero-cervical adenitis, and dehydration associated with an eating disorder. On Study Day 226, the subject was suspected of having left maxillary sinusitis (Study Days 226-233) for which the following was administered: penicillin G, ibuprofen, and omeprazole (all from Study Days 227-233).

Diagnostic testing included an x-ray, laboratory analysis, an abdominal and maxillary echo that showed a left maxillary sinusitis. Action taken with oteseconazole was not applicable since the event occurred post-oteseconazole exposure. The event was reported as resolved on Study Day 233.

Study Investigator's/Applicant's Impression: Neither the Study Investigator nor the Applicant assessed this case of sinusitis as being related to either fluconazole or oteseconazole maintenance therapy.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and the case narrative and agrees that the observed SAE was unrelated to oteseconazole exposure.

Subject (b) (6) (Oteseconazole) (PT: Cholecystitis Infective)

A 54-year-old White, non-Latino Romanian female with a past medical history noted for hypertension, obesity (BMI: 31.9) and a history of recurrent VVC. In the 12 months prior to study participation, the subject reported four episodes of acute VVC. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1 and the last dose of oteseconazole was administered on Study Day 86. The last dose of oteseconazole administered prior to the SAE was Study Day 79. The subject completed study participation on Study Day 350.

On Study Day 95, the subject was admitted into the hospital with complaints of severe abdominal pain and vomiting that had begun the day prior to admission. An abdominal ultrasound showed gallstones (cholelithiasis). The subject was diagnosed with acute gangrenous

cholecystitis (cholecystitis infective; Study Days 94-99) and received treatment with the following intravenous (IV) antibiotics:

- IV ampicillin (Study Day 95)
- IV gentamicin (Study Day 95-97)
- IV ceftriaxone (Study Days 95-97)
- IV metronidazole (Study Days 95-96)

A laparoscopic cholecystectomy was performed on Study Day 96 and the subject was discharged from the hospital, without any post-discharge medications, on Study Day 99. The Study Investigator recorded the SAE outcome as being resolved on Study Day 99. Action taken with oteseconazole was described as no change.

Study Investigator's/Applicant's Impression: Neither the Study Investigator nor the Applicant assessed the SAE (cholecystitis infective) as being related to either fluconazole or oteseconazole administration.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and the case narrative and agrees that the observed SAE was unrelated to oteseconazole exposure.*

Subject (b) (6) (Oteseconazole) (PT: Arthralgia)

A 38-year-old Black/African-American, non-Latino female with a past medical history noted for rheumatoid arthritis (since (b) (6)) and a history of recurrent VVC. In the 12 months prior to study participation, the subject reported three episodes of acute VVC. The only concomitant medication was paracetamol. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1. The last dose of oteseconazole and, similarly, the last dose prior to SAE onset, was Study Day 85. The subject completed participation in the study on Study Day 338.

The case narrative reports that on Study Day 315 the subject developed acute joint pain (arthralgia; Study Day 315 through 332) that was diagnosed, by a rheumatologist, as fibromyalgia, for which the subject was prescribed prednisone 20 mg twice daily from Study Day 322 to 324 as well as ferrous sulfate. Soon after starting these medications, the subject developed nausea, vomiting, diarrhea and tarry stools, presented to the emergency room (ER) and was admitted to the hospital (Study Day 324 through Study Day 327). On Study Day 326, the subject was placed on pantoprazole and an esophagogastroduodenoscopy was performed. The esophagogastroduodenoscopy demonstrated a small, intestinal tear that was repaired. SAE outcome of acute joint pain was reported as resolved on Study Day 332.

Study Investigator's/Applicant's Impression: Neither the Study Investigator nor the Applicant assessed arthralgia as being related to either fluconazole or oteseconazole administration. Neither did they think that the arthralgia was a flare of the subject's known RA. The outcome of the acute joint pain (arthralgia) was reported as resolved on Study Day 332.

Clinical Reviewer's Assessment: *The reviewer agrees that arthralgia is unrelated to oteseconazole, given a lack of a temporal association between the event and oteseconazole exposure. Based on review of the narrative, the reviewer considers the TEAE (PT: melena) to be the actual SAE. However, the reviewer suspects that this event was potentially precipitated by prednisone administration given without accompanying GI prophylaxis.*

Trial CL-012 Nonfatal Treatment-Emergent SAEs (Placebo)

Subject (b) (6) (Placebo) (PT: Pneumonia, Viral)

A 40-year-old Asian, non-Latino Belgian female with a past medical history significant for dust allergy and recurrent VVC, including a history of three acute VVC episodes in the 12 months prior to study enrollment. The subject was randomized into the study's Maintenance Phase and received the first dose of placebo on Study Day 1. The subject received the final dose of placebo on Study Day 85 and completed participation in the study on Study Day 347.

On Study Day 295, the subject was hospitalized with a treatment-emergent SAE coded to PT pneumonia, viral (Study Day 298 through 305), secondary to COVID-19 pneumonia as detected via a positive polymerase chain reaction. The subject received: ceftriaxone (Study Days 298 through 303) and hydroxychloroquine (Study Days 298 through 302).

Study Investigator's/Applicant's Impression: Neither the Study Investigator nor the Applicant assessed pneumonia, viral as being related to either fluconazole or placebo, due to a lack of a temporal association between receipt of placebo since this SAE occurred seven months post-drug exposure.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narratives and agrees that the observed SAE was not the result of placebo based on a lack of a temporal association and a lack of a biologically plausible explanation for this finding.

Subject (b) (6) (Placebo) (PT: Depression x4)

A 35-year-old White, non-Latino Belgian female with a relevant past medical history significant for two C-sections (b) (6) and recurrent VVC, including three episodes of acute VVC in the previous 12 months. Although the subject reported no prior to history of depression, depressive symptoms were identified. The subject was randomized into the study's Maintenance Phase and received the first dose of placebo on Study Day 1.

On Study Day 67, the subject was hospitalized for depression (Study Days 67 through 108) and was prescribed:

- Sertraline
- Amisulpride (a dopamine D2 receptor antagonist used the treatment schizophrenia),
- Prothipetyl hydrochloride (a neuroleptic azapenothiazine used to treat anxiety and agitation in psychotic syndromes).

The event was resolved on Study Day 108. However, the subject was re-hospitalized for exacerbations of depression a second, third, and fourth time on Study Days 172 through 197; Study Days 198 through 277; and Study Days 280 through 283, respectively, as manifested by aggressive behaviors, risk of self-harm, and/or suicidal thoughts. On each occasion, the subject required additional treatment with psychiatric medications.

Study Investigator's/Applicant's Impression: Both the Study Investigator and the Applicant believed each depressive episode the subject experienced was unrelated to placebo, and agreed the subject may have had an undiagnosed, underdiagnosed and/or undisclosed pre-existing psychiatric issue prior to study enrollment.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and participant narrative and agrees that the observed SAE was not due to receipt of placebo.*

Subject (b) (6) (Placebo) (PT: Severe Acute Respiratory Syndrome):

A 19-year-old White, non-Latino Romanian female with no prior medical history aside from a history of RVVC, with four episodes of acute VVC in the 12 months prior to study participation. The subject was randomized into the study and received the first dose of placebo on Study Day 1 and received the last dose of placebo on Study Day 85. The subject final dose of placebo prior to onset of SAE was also on Study Day 85.

On Study Day 296, the subject was diagnosed with SARS-CoV-2 (PT: severe acute respiratory syndrome [SARS]) (Study Days 292-306), upon demonstrating a positive polymerase chain reaction. The subject was asymptomatic but elected to be hospitalized due to inability to self-isolate at home. The subject was discharged from the hospital on Study Day 306. SAE outcome had resolved upon hospital discharge.

Study Investigator's/Applicant's Impression: Both the Study Investigator and Applicant attributed the subject's contracting SARS-CoV-2 as unrelated to receipt of placebo exposure due to a lack of a temporal relationship between the SAE and placebo, particularly since the subject had received the last dose of placebo approximately 7 months prior to SAE onset.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and case narrative and agrees that the observed SAE was not due to receipt of placebo given a lack of temporality, a lack of a biologically plausible mechanism of action, and since the event occurred during the global COVID-19 pandemic.*

Subject (b) (6) (Placebo) (PT: Myocarditis)

A 39-year-old Black/African-American, non-Latino female with several relevant medical conditions including hypertension (since (b) (6)), obesity (BMI 39.3); borderline diabetes (since (b) (6)), sarcoid (since (b) (6)), and a history of RVVC. Subject received the first dose of placebo on Study Day 1, and the final dose of placebo on Study Day 90.

On Study Day 11, the subject presented to the ER with a chief complaint of sharp, chest discomfort worsened with movement and upon sitting upright x 3 days and was hospitalized. The subject reported a recent history of an upper respiratory tract infection. An EKG showed <1 m ST elevations in lateral leads and a mild troponin leak peaking at 0.73. An echo on Study Day 13 showed a normal left and right ventricular function, a small pericardial effusion, and an interatrial septal 1 aneurysm. The subject was diagnosed with a treatment-emergent SAE (PT Myopericarditis) (Study Days 11-87) for which the following was administered:

- Oral methylprednisolone (Study Days 9-11)
- Ibuprofen (Study Day 11 – ongoing)
- Colchicine (Study Days 11-65)

The subject was discharged from the hospital on Study Day 15 with instructions to continue treatments for a myopericarditis.

Study Investigator's/Applicant's Impression: The Study Investigator assessed this reported SAE as being unrelated to the placebo but rather the sequelae of a prior upper respiratory infection (URI).

Clinical Reviewer's Assessment: Clinical reviewer agrees with the Study Investigator and Applicant that the reported event was unrelated to receipt of placebo but was the result of an URI.

Subject (b) (6) (Placebo) (PT: Breast Cancer)

A 43-year-old White, Latino female with a relevant past medical history notable for depression; fatigue; hypothyroidism; herpes simplex infection, and RVVC. The subject reported 12 previous episodes of acute VVC in the 12 months prior to study enrollment. The subject had a strongly positive family history of malignant tumors of the breast, thyroid, and stomach, as well as a family history positive for the breast cancer (BRCA) gene. The subject received the first dose of placebo on Study Day 1 and received the final dose of placebo on Study Day 87.

On Study Day 128, a bilateral MRI showed two suspicious masses. This was followed on Study Day 134 with a hospital consultation to discuss the abnormal MRI findings. On Study Day 141, the subject underwent an ultrasound guided right breast biopsy with pathology revealing an invasive duct carcinoma (IDC) grade 1, estrogen and progesterone receptor positive (PT: Breast cancer female; Study Days 150-162). Treatment options were discussed and the subject was prevented from pursuing a surgery due to COVID-19. The subject began tamoxifen treatment. The subject was terminated from the study on Study Day 162. The subject underwent a lumpectomy on Study Day 222 followed by radiation and chemotherapy with goserelin. SAE outcome was reported as not recovered at time of narrative report.

Study Investigator's/Applicant's Impression: The Study Investigator and Applicant determined that the observed SAE was unrelated to placebo exposure but rather was related to the history of a left sided breast nodule 8 months prior, a positive family history of malignant tumors and the BRCA gene mutation.

Clinical Reviewer's Assessment: Based on review of accompanying narrative and clinical data, the reviewer is in agreement with the Study Investigator and Applicant that the SAE (PT: breast cancer) was unrelated to receipt of placebo.

17.1.3. Trial CL-017 Nonfatal Treatment-Emergent SAEs

Oteseconazole Arm

Subject (b) (6) (Oteseconazole) (PTs: Cerebrovascular Accident, Deep Vein Thrombosis, Pulmonary Embolism, Anemia, and Retroperitoneal Hemorrhage)

A 38-year-old White, non-Latino American female with a past medical, psychiatric, and surgical history notable for s/p post-partum pulmonary embolism (in (b) (6)); hypertension (since (b) (6)); depression (since (b) (6)); ADHD (since (b) (6)); gallstones s/p cholecystectomy (b) (6) s/p tubal ligation (b) (6) recurrent bacterial vaginosis (since (b) (6)); and RVVC (since (b) (6)). Within the 12 months prior to study participation, the subject reported 5 episodes of acute VVC.

Key concomitant medication included:

- Psychiatric medications: bupropion (Study Days -730 to 187), topiramate (Study Days 170-187), fluoxetine (Study Days 189 – ongoing)
- Promethazine (Study Days 187 - ongoing)
- Fexofenadine (Study Days 187 – ongoing)
- Heparin drip (Study Days 187-195)
- Apixaban (Study Days 195-197, Study Days 206- ongoing)

The subject was randomized on Study Day 1 into the oteseconazole arm when the subject received the first induction dose of oteseconazole. The subject received the final dose of oteseconazole on Study Day 90 prior to all reported SAEs. The subject completed Study CL-017 on Study Day 373.

On Study Day 187, the subject developed a headache (PT: migraine; Study Days 185-187) with associated right-sided hemiparesis (weakness) (Study Days 187-189) for which the subject presented to the hospital. A noncontrast CT of the head showed an acute thrombosis of cerebral venous sinuses with subarachnoid and parenchymal hemorrhages coded to nonfatal SAE (PT: cerebrovascular accident; Study Days 187-190). CT angiogram of head and neck demonstrated an interval expansion of an intraparenchymal hemorrhage. The subject was placed on a heparin drip for the cerebrovascular accident from Study Days 168-176. Additional stroke work-up on Study Day 188, included a transcranial doppler ultrasound and spinal cerebral arteriogram on Study Day 189 that demonstrated total occlusion of several cerebral venous sinuses for which the subject underwent a thrombectomy on Study Day 189.

The subject was reported to have a GI bleed (PT: melena) on Study Days 197-272 requiring discontinuation of anticoagulation and a red blood cell transfusion (Study Days 197-272). A CT abdomen and pelvis revealed a right pelvic and rectus sheath hematoma with bilateral pulmonary emboli (PT: retroperitoneal bleed; Study Day 197) (PT: pulmonary emboli; Study Days 199-206). An esophagogastroduodenoscopy (EGD) with biopsy was performed. (PT: anemia). On Study Day 199, a bilateral venous ultrasound of lower extremities showed a DVT of the right lower extremity (PT: deep vein thrombosis; Study Days 199-206). No DVT was not found in the left lower extremity. The subject was eventually transitioned to the oral anticoagulant apixaban for treatment of DVT, PE, and as DVT prophylaxis. An inferior vena cava filter was placed on Study Day 201. Repeat imaging obtained on Study Day 214 showed resolving intraparenchymal hemorrhages and new and persisting thrombi in the cerebral venous system. The subject had a nonserious TEAE of dysphagia (Study Days 189-199). All SAE events were eventually reported as resolved. The subject was discharged from the hospital on Study Day 206.

Study Investigator's/Applicant's Impression: The Study Investigator assessed all SAEs as being unrelated and unexpected due to a lack of temporal relatedness between the described events and oteseconazole exposure (PTs: cerebrovascular accident, deep vein thrombosis, pulmonary embolism, and retroperitoneal hemorrhage). Moreover, that patient had a pre-existing history of post-partum PE.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narrative and agrees that the observed SAEs were not the result of oteseconazole exposure. The participant/patient did have a prior history of post-partum PE. It is unclear whether the participant had an underlying hypercoagulable condition. Subject did not appear to be on birth

control. The rectal sheath and retroperitoneal hemorrhage were iatrogenic given the administration of anti-coagulant therapy in the setting of embolic stroke with persistent thrombi.

Subject (b) (6) (Oteseconazole) (PT: Appendicitis)

A 66-year-old White, non-Latino American female with a past medical history notable for genital herpes simplex and recurrent VVC, with a total of three acute VVC episodes within the 12 months prior to study enrollment. The subject was randomized into the oteseconazole arm of the Induction Phase on Study Day 1, and the subject received the first dose of oteseconazole this same day. The subject received the final dose of oteseconazole on Study Day 85. The subject completed participation in the study on Study Day 363.

Key pre-enrollment concomitant medications included:

- Valacyclovir (Study Days -2191 – ongoing);
- Estrogens conjugated (Study Days 186 – ongoing).

On Study Day 193, the subject developed right lower quadrant abdominal pain, nausea and abdominal bloating for which the subject was hospitalized and diagnosed with an acute uncomplicated appendicitis (Study Day 193-194). The subject underwent an appendectomy on Study Day 193 and was discharged from the hospital the following day. While hospitalized the subject received:

- IV morphine (Study Days 193-194),
- IV ondansetron (Study Days 193-194),
- Several antibiotics including ertapenem (Study Day 193);
- Piperacillin-tazobactam (Study Day 193-194).

Study Investigator's/Applicant's Impression: The Study Investigator assessed SAE as being unrelated due to a lack of temporal association and a lack of a causal mechanism between the described events and oteseconazole administration (PT: appendicitis).

Clinical Reviewer's Assessment: The clinical reviewer has reviewed the accompanying data and narrative and agrees with the Study Investigator and Applicant that the observed SAE was unrelated to oteseconazole exposure.

Trial CL-017 Nonfatal Treatment-Emergent SAEs (Fluconazole/Placebo)

Subject (b) (6) (Fluconazole/Placebo) (PT: Pneumonia)

A 23-year-old White, non-Latino American female with a past medical and psychiatric history notable for anxiety (since (b) (6)); post-traumatic stress disorder (since (b) (6)); bipolar disorder, depression; and a history of recurrent VVC, with a total of six acute VVC episodes within the 12 months prior to study participation, was enrolled into the Induction Phase of the study on Study Day 1. The subject was randomized into the fluconazole/placebo arm and received the first dose of placebo that same day. The subject remained in the Induction Phase of CL-017 through Study Day 16 and entered into the Maintenance Phase of Study CL-017 that same day. The subject received the final dose of placebo on Study Day 86. Participation in the study ended on Study Day 277 after being lost to follow-up. The subject was under the care of a psychiatrist.

Concomitant medications included:

- Amitriptyline (Study Days -5844 – ongoing);
- Butalbital, caffeine paracetamol (Study Days -5844 – ongoing);
- Ondansetron (Study Days -5844 – ongoing);
- Sumatriptan (Study Days -5844 – ongoing);
- Alprazolam (Study Days -730– ongoing);
- Tizanidine (Study Days -730 – ongoing);
- Sertraline (Study Days -730 to 23; Study Day 23- ongoing);
- Desogestrel/ethinyl estradiol (Study Day -374 – ongoing);
- Prazosin (Study Day 23 -ongoing)

The subject was hospitalized on Study Day 69 with a pneumonia (Study Days 69-72) due to an accidental overdose after the subject was found at home unresponsive with no pulse requiring cardiopulmonary resuscitation (CPR) and an intensive care unit (ICU) admission. A chest x-ray (CXR) on admission showed no infiltrates. A drug screen was positive for benzodiazepine, cannabis, and cocaine. The subject denied homicidal and suicidal ideation.

Study Investigator's/Applicant's Impression: The Study Investigator and Applicant assessed SAE as an aspiration pneumonia secondary due to an accidental overdose, since the subject had ingested sertraline (Zoloft), prazosin (for treatment of high blood pressure), and alprazolam (Xanax) all superimposed upon recreational drug use. They believed the subject's underlying psychiatric history was a contributor to the reported SAE.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narrative and agrees with the Study Investigator and Applicant that the observed SAE was unrelated to receipt of placebo but likely the result of a participant with a polysubstance abuse and underlying mental health issues.

17.1.4. Trial CL-006 Nonfatal Treatment-Emergent SAEs

Oteseconazole Arm

Subject (b) (6) (Oteseconazole 300-mg x24 Weeks) (PT: Meningitis, Viral)

A 20-year-old White, non-Latino female with a past medical history most notable for supraventricular tachycardia/Wolff-Parkinson-White syndrome (diagnosed (b) (6)), s/p heart ablation (diagnosed (b) (6)); left breast solitary mass (diagnosed September (b) (6)); and a history of RVVC (since (b) (6)). Participant was randomized into and received the first dose of oteseconazole 300-mg x 24 weeks on Study Day 1. The subject received the last dose of oteseconazole on Study Day 168. The subject completed the study on Study Day 329.

On Study Day 187, the subject was admitted to the hospital with fever, nausea, vomiting, epigastric pain, and intractable headaches for two days. A work-up including an abdominal ultrasound, a noncontrast CT of the head and brain, CXR, and a magnetic resonance angiogram (MRA) was unremarkable. Following a lumbar puncture, the subject was diagnosed with viral meningitis. Cerebrospinal fluid (CSF) cultures were negative.

Concomitant medications included:

- Ceftriaxone (Study Days 187- 190)
- Vancomycin (Study Days 188 -190)
- Ondansetron
- Promethazine
- Enoxaparin
- Acyclovir (high dose)
- Sulfate
- Lorazepam

The event was considered resolved on Study Day 191 and the subject was discharged from the hospital that same day with a discharge diagnosis of viral meningitis (Study Day 187-191).

Study Investigator's/Applicant's Impression: The Study Investigator assessed the event as being unrelated to oteseconazole administration, given a lack of a temporal association between the event and oteseconazole exposure.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed the accompanying data and the subject narrative and agrees that the observed SAE was unrelated to oteseconazole exposure for reasons of a lack of a temporal association and a lack of a causal relationship the between event and the study drug.

Subject (b) (6) (Oteseconazole 300-mg x24 Weeks) (PT: Bronchopneumonia [Hypotension])

An 18-year-old White, non-Latino female with a past medical history most notable for anxiety, treated with benzodiazepine diazepam, recurrent urinary tract infections (UTIs) (since (b) (6)), s/p motor vehicle accident (b) (6) with chronic back pain on chronic opiates, and a history of recurrent VVC (since (b) (6)). Subject was randomized into and received the first dose of oteseconazole 300-mg x 24 weeks on Study Day 1. The subject received the last dose of oteseconazole on Study Day 162. The subject completed the study on Study Day 305, however, the subject failed to complete the entire study due to being lost to follow-up.

On Study Day 216, the subject presented to a hospital emergency room with a complaint of bilateral flank pain, fever, dysuria, nausea, vomiting, dizziness, and fatigue. A CXR showed bilateral patchy infiltrates with bilateral bronchopneumonia (Study Days 216-218). A CT of the abdomen and pelvis showed left > right basilar consolidation. Participant had persistent orthostatic hypotension for which the subject was administered a total of 4 liters of 0.9% normal saline. In the ED, the subject received ibuprofen, ondansetron, azithromycin, metronidazole, and ceftriaxone sodium. The following day, the subject was admitted under observation to the ICU where the subject was observed for persistent dizziness over 12 hours. Staff was initially concerned for pneumonia or aspiration given CXR findings and shortness of breath. Hypotension resolved on Study Day 218. Prior to being discharged from the hospital, the subject was counseled on narcotics use and the risk of sedation and constipation. Discharge diagnoses included constipation, chronic pain, anxiety, depression, and hematuria. During the study, this subject was additionally recorded as having the following nonserious TEAEs: constipation, arthralgia, back pain, musculoskeletal pain, nausea, flank pain, anemia, dysuria, and bronchopneumonia.

Study Investigator's/Applicant's Impression: The Study Investigator assessed the event as being unrelated to oteseconazole administration, given the absence of a temporal or causal relationship between the event and oteseconazole administration. In addition, there was an alternate biologically plausible alternate explanation for the observed event.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed the subject's accompanying data and narratives and agrees that the observed SAE was unlikely the result of oteseconazole exposure. It appears that the subject's refractory hypotension was related to opiate abuse and further exacerbated by superimposed benzodiazepine abuse. Certain opiates can cause orthostatic hypotension which may result in dizziness. Opiates are also associated with constipation. Diazepam can cause hypotension as well. If the subject experienced alteration in mental status in the setting of opiate misuse, subject could very well have aspirated. The reviewer thinks that the described SAE would have more appropriately been coded as an accidental overdose.*

Subject (b) (6) (Oteseconazole 300-mg x24 Weeks) (PT: Appendicitis)

A 45-year-old White, non-Latino female with a past medical history most notable for irritable bowel syndrome (since (b) (6)); cervical intraepithelial neoplasia-2 s/p cryotherapy; abnormal pap smear with low grade squamous intraepithelial lesion (LGSIL), s/p colposcopy (b) (6) genital herpes (b) (6) and a history of RVVC. Subject was randomized into and received the first dose of oteseconazole 300-mg x 24 weeks on Study Day 1. Subject received the last dose of oteseconazole on Study Day 167. Subject completed the study on Study Day 350.

The subject was admitted into the hospital, on Study Day 115 with appendicitis (Study Days 115-122), and underwent a laparoscopic appendectomy. The subject was treated with cefazolin and IV fluids. The appendicitis resolved on Study Day 122 and the subject was discharged from the hospital in no acute distress the following day on Study Day 123. The subject was also reported to have a nonserious adverse event of headache.

Investigator's/Applicant's Impression: The Investigator assessed the event as being unrelated to oteseconazole administration.

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed the accompanying subject data and the subject narrative and agrees that the observed SAE was coincidental and unrelated to oteseconazole exposure despite the temporal association with oteseconazole therapy.*

Subject (b) (6) (Oteseconazole 150-mg x12 Weeks) (PT: Abdominal Pain/Pancreatitis)

A 36-year-old White, Latino female with a past medical history most significant for depression (since (b) (6)), anxiety, chronic pancreatitis (since (b) (6)), s/p gallbladder removal (b) (6) pre-diabetes controlled with diet (since (b) (6)), rheumatoid arthritis, systemic lupus erythematosus (since (b) (6)), migraines, and a history of recurrent VVC. The was randomized into the study and received the first dose of oteseconazole 150-mg x 12 weeks on Study Day 1. Final dose of oteseconazole received on Study Day 22 due to premature discontinuation of study treatment secondary to SAE (pancreatitis). The subject completed their participation in the study on Study Day 337.

On Study Day 25, the participant developed abdominal pain, nausea, emesis, lightheadedness, and collapsed to the floor. Subject presented to the ER and was hospitalized. A CT of the

abdomen and pelvis with contrast was obtained and was largely unremarkable. “At presentation, the subject’s amylase was mildly increased at 141 IU/L (reference range 28-100 IU/L) and lipase was mildly increased at 58.0 U/L (reference range 10-55 U/L). The subject also tested positive for cannabinoids in the urine.” On Study Day 26, the subject received an ultrasound of the abdomen that was normal except for a surgically removed gallbladder, “with presumed mild compensatory dilatation of the biliary system.” The pancreas was partially visualized and grossly unremarkable. “An magnetic resonance cholangiopancreatography showed no filling defect, choledocholithiasis, biliary stricture, or obstruction was noted.”

Two days later, Study Day 28, an endoscopic retrograde cholangiopancreatography with sphincterotomy was performed, and the subject was diagnosed with acute pancreatitis (Study Days 25-33). The subject was treated with various concomitant medications notably including hydromorphone, morphine sulfate, cefazolin, indomethacin, pancrelipase, sucralfate, esomeprazole, famotidine, and cholestyramine. Study drug treatment was discontinued on Study Day 22. Subject was discharged from the hospital with resolution of pancreatitis on Study Day 33. The Study Investigator determined that the acute episode of pancreatitis was unlikely related to oteseconazole exposure.

The subject experienced a moderate SAE of abdominal pain on Study Day 81 (Study Days 81-84) for which subject presented to the ER with an inability to tolerate any oral intake. The subject was hospitalized and underwent a work-up that was unrevealing. While hospitalized, the subject received hydromorphone, morphine, tramadol, pancrelipase, sucralfate, and pantoprazole. Subject was discharged home on Study Day 84 with reported resolution of abdominal pain.

Study Investigator’s/Applicant’s Impression: The Investigator assessed the two events as being unrelated to oteseconazole therapy.

Clinical Reviewer’s Assessment: *Clinical reviewer has reviewed accompanying data and subject narrative and agrees that the observed SAEs were most likely unrelated to oteseconazole exposure. These SAEs occurred in a subject with a known history of chronic pancreatitis and apparent chronic GI issues. In addition, the subject had multiple other co-morbid conditions. The initial case of pancreatitis demonstrated only mild lipase elevations with largely unremarkable imaging, and resulted in discontinuation of the study drug. The second SAE occurred following discontinuation of oteseconazole exposure and was unlikely related to oteseconazole administration.*

CL-006 Narratives (Placebo)

Subject (b) (6) (Placebo) (PT: Paronychia)

A 27-year-old White, non-Latino female with a past medical history significant for obesity (BMI 37.1), depression (since (b) (6)), genital herpes (since (b) (6)), and a history of RVVC was randomized into Study CL-006 and received the first dose of placebo on Study 1. On Study Day 174, subject received the final dose of placebo and completed the study on Study Day 337.

The subject reported developing a left thumb cellulitis with phlebitis on Study Day 299 for which the subject presented to and was discharged from the ER on Study Day 300, after receiving antibiotics and an incision and drainage was attempted. The subject denied trauma and plant or chemical exposures. On Study Day 301, the subject presented to primary physician’s office febrile to 103 F and was instructed to return to the ER where the subject was noted to have

erythematous streaking of a left upper extremity cellulitis and was diagnosed with SAE (PT: herpetic cellulitis). The subject was discharged from the ER to home that same day only to develop worsening swelling, redness, discoloration and increased streaking that had spread to their forearm.

On Study Day 302, subject was admitted and treated with vancomycin, ibuprofen, and valacyclovir. On exam, subject was noted to “have 3 to 4 small pustular formations superior to the nailbed of her left thumb, erythematous tracking similar to phlebitis to the elbow.” Subject was discharged to home on Study Day 304. The herpes simplex outbreak (PT: Paronychia; Study Days 301-304) was being resolved.

Study Investigator’s/Applicant’s Impression: The Investigator assessed the event as being unrelated to receipt of placebo.

Clinical Reviewer’s Assessment: *Clinical reviewer has reviewed accompanying data and narratives and agrees that the observed SAE was not the result of receipt of placebo. The subject quite possibly had a herpetic whitlow resulting in cellulitis and lymphangitis. Unclear if SAE was the result of auto-inoculation since there was no mention of an ongoing genital herpes outbreak, however, subject does have a known history of genital herpes.*

17.2. TEAEs Leading to Discontinuation of Study Drug

17.2.1. Trial CL-011 TEAEs Leading to Discontinuation of Study Drug

Subject (b) (6) (Oteseconazole 150-mg) (PT: Vaginal Infection)

A 34-year-old White, non-Latino female with a past medical history most significant for spontaneous abortions (b) (6) a drug hypersensitivity reaction to sulfonamides (b) (6) endometriosis (b) (6) s/p laparoscopy (b) (6) uterine dilatation and curettage (b) (6) anemia (b) (6) and a history of recurrent VVC, with four reported episodes of VVC in the previous 12 months. The subject was randomized into the study’s Maintenance Phase and received the first dose of oteseconazole on Study Day 1. The final dose was received on Study Day 29.

On the Study Day 14 visit, the subject was documented as having a total vaginal signs and symptoms score of 5 and a positive potassium hydroxide prep. The subject was diagnosed with a recurrent episode of VVC, vaginal infection (Study Days 19-37) for which the subject was given a single dose of fluconazole 150-mg as per protocol. On Study Day 19, subject was reported as having a repeat episode of acute vaginitis for which was treated with a boric acid suppository, fluconazole, nystatin cream, and terconazole cream.

The subject was prematurely discontinued from the study at the Early Termination visit on Study Day 37. “The site commented that the reason for the subject terminating early from the study as subject is unwilling to refrain from using exclusionary/prohibited medications”.

Study Investigator’s/Applicant’s Impression: The Investigator determined the event vaginal infection as being unrelated to oteseconazole exposure

Clinical Reviewer's Assessment: *Clinical reviewer has reviewed accompanying data and narratives and considers the described TEAE to be an oteseconazole treatment failure as opposed to a TEAE.*

17.2.2. Trial CL-012 TEAEs Leading to Discontinuation of Study Drug

Subject (b) (6) (Oteseconazole) (PT: Blister)

A 25-year White, non-Latino Romanian female with a past medical noted solely for recurrent VVC, with four episodes of acute VVC reported in the 12 months prior to study enrollment. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1. Subject took oteseconazole for 6 days. Subject received the last dose of oteseconazole on Study Day 7 and discontinued participation in the study on Study Day 24.

On Study Day 5, the subject reportedly developed blisters/vesicles (Study Days 5-7) which resolved on Study Day 7. There were no reported concomitant medications. The subject refused to return to the study site for the final visit but reported that “[she] had never had this problem in the past and did not identify any other possible factor for the vesicles.”

Study Investigator's/Applicant's Impression: The Study Investigator assessed the reported adverse event as moderate in intensity and possibly related to oteseconazole exposure. The Study Investigator reported that the incident resolved after two days and required no treatment.

Clinical Reviewer's Assessment: *Based on the limited evidence presented and the temporal relationship between administration of oteseconazole and the AE onset, the clinical reviewer cannot exclude the possibility that the reported event was related to oteseconazole exposure. Importantly, however, given the rapidity with which the event resolved, the reported TEAE did not appear to be a severe cutaneous reaction such as Stevens-Johnson Syndrome.*

Subject (b) (6) (Oteseconazole 150-mg) (PT: Abdominal distension)

A 42-year White, Latino American female with a past medical noted for mammoplasty (b) (6) hypothyroidism (b) (6) and a history of recurrent VVC. The subject reported three episodes of acute VVC within the 12 months prior to study enrollment. The only reported concomitant medication was levothyroxine 88 micrograms daily. The subject was randomized into the Maintenance Phase and received the first dose of oteseconazole on Study Day 1. The subject received the last dose of oteseconazole on Study Day 29. The subject entered the study extension phase on Study Day 343.

Beginning on Study Day 18, the participant complained of abdominal bloating and distention (Study Days 18- 27). The subject voluntarily discontinued the oteseconazole due to abdominal distension and elected not to resume oteseconazole. The subject remained in the study through Week 48.

Study Investigator's/Applicant's Impression: The Investigator assessed the reported adverse event as moderate in intensity and possibly related to the oteseconazole.

Clinical Reviewer's Assessment: *Based on the limited evidence presented and the temporal relationship between oteseconazole exposure and AE onset, the clinical reviewer cannot exclude*

the possibility that the reported event was related to oteseconazole use. The reviewer agrees that the event is potentially related to the oteseconazole.

Trial CL-012 TEAEs Leading to Discontinuation of Study Treatment

Subject (b) (6) (Placebo) (PT: Influenza)

A 60-year-old White, non-Latino Romanian female with a relevant past medical history notable for hypertension (since (b) (6)), atrial fibrillation (since (b) (6)), morbid obesity (BMI 45.7), and a history of recurrent VVC with a reported three episodes of acute VVC within the 12 months prior to study participation. The subject was randomized into the Maintenance Phase of the study on Study Day 1 and received the first dose of placebo that same day. Participation in the study ended on Study Day 37 reportedly due to subject noncompliance with a reported <80% compliance with placebo.

Subject was diagnosed with influenza on Study Day 25 (Study Days 25-36) and reportedly recovered from the event on Study Day 36. Action taken was that the subject withdrew from study drug (placebo).

Study Investigator's/Applicant's Impression: The Study Investigator assessed this reported case of influenza as being unrelated to placebo exposure.

Clinical Reviewer's Assessment: Clinical reviewer has reviewed accompanying data and narratives and considers the described TEAE to be unrelated to placebo administration.

17.2.3. Trial CL-017 TEAEs Leading to Discontinuation of Study Drug

Subject (b) (6) (Oteseconazole 150-mg) (PT: Allergic Dermatitis)

A 38-year-old White, non-Latino female (USA) with a prior medical history most noted for metrorrhagia (since (b) (6)); dysmenorrhea (since (b) (6)); and a history of RVVC, with five prior episodes of acute VVC within the 12 months prior to study enrollment. The subject was randomized into the oteseconazole arm of the induction phase of Study CL-017 and received the first dose of oteseconazole that same day (Study Day 1).

Subject presented to the emergency room with a rash that same day (Study Day 1) for which the subject was given Zofran 4 mg IV x1, benadryl 50-mg IV x 1, and 0.9% normal saline (allergic dermatitis Study Days 1-16). Subject returned to the ER the following day (Study Day 2) for repeat treatment of the rash and received famotidine 40-mg IV x 1, diphenhydramine 50-mg IV x 1, dexamethasone 10-mg IV x1.

Subject was discharged to home with the following:

- Methylprednisolone 4-mg (b) (6)
- Hydroxyzine 25-mg three times daily (b) (6) and
- Famotidine 20-mg twice daily (b) (6)

The subject presented early to the Day 14 scheduled visit on Study Day 4 (b) (6) where the rash was evaluated and described as "mild pink skin rash on trunk and extremities."

The subject was initially considered as an “Induction Failure.” The subject discontinued participation in the study through Study Day 36.

Study Investigator’s/Applicant’s Impression: On January 22 2020, the Study Investigator noted, “Due to timing of onset of AE PI states this AE is related to IP; reintroduction of IP is too dangerous and PI will not re-challenge this patient.” This subject was noted as terminating early from the due to an adverse event. The Study Investigator recorded the adverse event of “diffuse allergic eruption (erythema and macular rash).”. The subject did not return to the site for this study after Study Day 4 (b) (6)”

Clinical Reviewer’s Assessment: Clinical reviewer agrees that the described TEAE resulting in discontinuation of oteseconazole was related to the study treatment.

17.2.4. Trial CL-006 TEAEs Leading to Discontinuation of Study Drug

Subject (b) (6) (Oteseconazole 300-mg x 12 Weeks) (PT: Dermatitis Allergic)

A 25-year-old woman non-Latino female described as “Other” with a past medical history most significant for chronic vaginal infections (since (b) (6)) and bacterial vaginosis (since (b) (6)). The subject was randomized into the study and received the first dose of oteseconazole 300-mg x 12 weeks on Study Day 1. The subject received the final dose of oteseconazole on Study Day 7 after developing a systemic rash/allergic reaction to study drug. Subject completed participation in the study on Study Day 323.

According to the participant narrative, on Study Day 9, the subject experienced a moderate TEAE of dermatitis allergic (Study Days 9-45) for which subject was treated with prednisone. The described event resulted in the subject prematurely and permanently withdrew from study drug.

Investigator’s/Applicant’s Impression: The Study Investigator and Applicant assessed this event of as being related to oteseconazole exposure.

Clinical Reviewer’s Assessment: Clinical reviewer has reviewed the accompanying data and subject narrative and agrees with the Study Investigator’s and Applicant’s assessment that the observed TEAE (PT: dermatitis allergic) was related to receipt of oteseconazole.

17.3. Adverse Events of Special Interest-- Narratives

17.3.1. Hepatotoxicity

CL-011

Subject CL-011 (b) (6) (Oteseconazole)

A 35-year-old white, non-Latino Bulgarian female with a past medical history of 3 prior episodes of RVVC ([Table 171](#)). The subject received the initial dose of oteseconazole on Study Day 1. The last dose of oteseconazole was administered on Study Day 86.

This subject had **no reported TEAEs** and was **not on any concomitant medications** either prior to or during the study.

Subject CL-011 (b) (6) **(Oteseconazole)**

A 38-year-old Japanese, non-Latino female with several past medical conditions most notably, multiple bacterial vaginosis (BV) episodes and a history of RVVC ([Table 172](#)). The subject received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole was on Study Day 85.

Concomitant medications included:

- Levocetirizine reportedly for vulvovaginal pruritus (Study Days 28-29) and pollinosis (Study Day 287 – ongoing);
- Estriol (Study Day 43 -49);
- Alisma plantago aquatica (choreito- Japanese traditional medication used for hemorrhagic cystitis) and cefcapene HCL (third generation cephalosporin) for cystitis (Study Days 112 - 115 and Study Days 2020 - 205)
- Intravaginal benzalkonium chloride and intravaginal chloramphenicol for BV (Study Days 112 -115).

Subject sustained a total of seven nonserious, TEAEs coded under the following PTs:

- Vulvovaginal pruritus (Study Days 25 - 30);
- Bacterial vaginosis (Study Days 108 - 115);
- Cystitis x 2 (Study Days 108 - 115 and Study Days 202 -205);
- Blood triglycerides increased (Study Day 177 - 183);
- AST increased (Study Days 202-205);
- Blood creatine phosphokinase increased (Study Days 202 -221).

***Clinical Reviewer's Conclusions:** Subject's transaminase elevations appear to coincide with creatine phosphokinase (CPK) elevations.*

Subject CL-011 (b) (6) **(Oteseconazole)**

A 43-year-old White, non-Latino Polish female with a past medical history most notable solely for a history of RVVC ([Table 173](#)). The subject received the initial dose of oteseconazole on Study Day 1. The last dose of oteseconazole was administered on Study Day 87.

Concomitant medication included Yasmin (ethinyl estradiol/drospirenone), an oral contraceptive pill. The subject had no reported TEAEs.

Subject CL-011 (b) (6) **(Oteseconazole)**

A 50-year-old Black/African-American, non-Latino female with a past medical history most notable for genital herpes and a history of RVVC ([Table 174](#)). The subject received initial dose of oteseconazole on Study Day 1. The last dose of oteseconazole was administered on Study Day 87.

The subject's sole concomitant medication both prior to and during the study was valacyclovir (Valtrex) for a history of genital herpes.

NDA 215888
Vivjoa (oteseconazole)

Subject reportedly had a single nonserious TEAE coded to PT: blood creatine phosphokinase (Study Day 45 through 56).

Clinical Reviewer's Conclusions: *Subject's transaminase elevations appear to coincide with CPK elevations.*

APPEARS THIS WAY ON ORIGINAL

Table 171. Results for Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -16)	Baseline (D 1)	Day 14 (D 16)	Wk 6 (D 36)	Wk 12 (D 99)	Wk 18 (D 134)	Wk 24 (D 163)	Wk 30 (D 198)	Wk 36 (D 266)	Wk 48 (D 337)
ALT (≤ 33)	32	33	117	13	•	9	8	11	17	•
AST (≤ 31)	20	14	42	15	24	13	14	21	30	•
Tbili (≤ 1.2)	0.3	0.3	0.3	0.4	0.7	0.3	0.5	0.7	0.4	•
Dbili (0-0.3)	0.1	0.1	0.1	0.2	•	0.1	0.2	•	0.2	•
Alk phos (35-104)	57	79	172	61	51	31	47	58	63	•

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; Wk, week

Table 172. Results for Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -19)	Baseline (D 1)	Day 14 (D 13)	Wk 6 (D 43)	Wk 12 (D 85, 97 unsch)	Wk 18 (D 140)	Wk 24 (D 177, 183 unsch)	Wk 30 (D 202, 221)	Wk 36 (D 252)	Wk 42 (D 287)	Wk 48 (D 377)
ALT (≤ 33)	26	20	14	14	18 (13, unsch)	14	•	39	17	14	12
AST (≤ 31)	29	20	21	21	22 (17 unsch)	16	•	96	21	17	21
Tbili (≤ 1.2)	0.2	0.3	0.8	0.6	0.4 (0.3, unsch)	0.6	0.1	0.5	0.3	0.2	0.6
Dbili (0-0.3)	0.1	0.1	0.3	0.2	• (0.1, unsch)	0.2	•	0.2	0.1	0	0.2
Alk phos (35-104)	70	36	48	51	46 (59, unsch repeat)	47	66	55 (45, unsch repeat)	52	53	46

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; Wk, week

Table 173. Results for Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -16)	Baseline (D 1)	Day 14 (D 23)	Wk 6 (D 44)	Wk 12 (D 62)	Wk 18 (D 115)	Wk 24 (D 162)	Wk 30 (D 202)	Wk 36 (D 229)	Wk 42 (D 285, 289)	Wk 48 (D 323)
ALT (≤33)	17	12	12	14	12	22	13	13	28	46 (29, unsch)	25
AST (≤31)	15	21	14	19	17	32	15	14	25	99 (17, unsch)	25
Tbili (≤1.2)	0.4	0.3	0.3	0.3	0.2	0.5	0.2	0.4	0.7	0.5 (0.4, unsch)	0.3
Dbili (0-0.3)	0.2	0.1	0.1	0.1	0	0.2	0	0	0.2	0.2 (0.1, unsch)	0.1
Alk phos (35-104)	58	47	●	56	61	40	101	105	35	39/ (106, unsch)	46

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week

Table 174. Results for Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -12)	Baseline (D 1)	Day 14 (D 17)	Wk 6 (D 45, 49 unsch)	Wk 12 (D 88)	Wk 18 (D 133)	Wk 24	Wk 30 (D 210)	Wk 36 (D 274)	Wk 42 (D 303)	Wk 48/ (D 238)
ALT (≤33)	11	13	10	65 (28, unsch)	12	11	●	25	16	13	19
AST (≤31)	14	16	12	142 (23, unsch)	13	18	●	18	20	17	23
Tbili (≤1.2)	0.5	0.4	0.5	0.6 (0.8, unsch)	0.2	0.5	●	1	0.3	0.7	0.7
Dbili (0-0.3)	0.1	0.1	0.1	0.2 (0.2 unsch)	0	0.2	●	0.2	0.1	0.1	0.1
Alk phos (35-104)	45	43	41	44 (39 unsch)	40	46	●	47	44	44	41

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

CL-012

Subject CL-012- (b) (6) **(Oteseconazole)**

A 52-year old White, non-Latino female with an otherwise unremarkable past medical history aside for an irregular heart rate and a history of RVVC ([Table 175](#)). The subject received their first dose of oteseconazole was on Study Day 1. Subject received final dose of oteseconazole on Study Day 85.

The subject's concomitant medications included:

- Propafenone, an anti-arrhythmic (since (b) (6) ongoing);
- Nadolol, a beta-blocker (since (b) (6) ongoing);
- Metronidazole for bacterial vaginosis (Study Days 213-217); and
- Ampicillin reportedly for bacterial vaginosis (Study Days 335-349).

The subject was reported to have four nonserious TEAEs coded to the following PTs and none of which were deemed by the Study Investigator to be related to the study drug. No changes to the study drug were made due to any of the reported TEAEs.

- Bacterial vaginosis x 2 (Study Days 210 to 215 and 335 ongoing);
- Vulvovaginal discomfort (Study Days 228-232); and
- Hepatic elevations (Study Days 233-267).

Clinical Reviewer's Conclusions: *Subject's transaminase elevations appear to coincide with the start of metronidazole for bacterial vaginosis (Study Day 213-217) but continued to peak several days after discontinuation of metronidazole—suggesting that this is an incidental finding.*

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Table 175. Results for Subject CL-012 (b) (6)

Results (Reference Range)	Screening (D -14)	Baseline (D 1)	Day 14 (D 15)	Wk 6 (D 43)	Wk 12 (D 93)	Wk 18 (D 134)	Wk 24 (D 162)	Wk 30 (D 213/230)	Wk 36 (D 265)	Wk 42 (D 281)/	Wk 48 (D 335)
ALT (≤33)	23	35	29	24	27	26	45	56/ (197, unsch)	64	46	40
AST (≤31)	17	25	19	17	19	18	32	40/ (144, unsch)	35	32	27
Tbili (≤1.2)	0.3	0.3	0.3	0.3	0.2	0.3	0.4	0.4/0.4 unsch	0.5	0.4	0.4
Dbili (0-0.3)	0.1	0	0	0	0	0	0	0/0.1 unsch	0.1	0.1	0.1
Alk phos (35-104)	59	61	59	68	60	57	68	55/60 unsch	54	58	56

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week

CL-017

Subject CL-017 (b) (6) (Oteseconazole)

A 36-year-old White, Latino female with a past medical history most notable for Grave's disease (b) (6) /hyperthyroidism (b) (6) HPV and cervical dysplasia (b) (6) vitamin D deficiency (b) (6) all in addition to a history of RVVC ([Table 176](#)). The subject received the first dose of oteseconazole on Study Day 1 and received the final dose of oteseconazole on Study Day 85.

Relevant concomitant medications including those begun prior to treatment and ongoing upon the completion of treatment:

- Fluconazole 150-mg once for yeast infection (Study Days 114 to 115);
- Theraflu once for nasal congestion (Study Day 136);
- Intravaginal metronidazole 37.5-mg once for bacterial vaginosis infection (Study Day 189);
- One liter IV normal saline x 1 (for “replacement of lost body fluids and salts”);
- Phentermine for weight loss (beginning Study Day 268 ongoing);
- Amoxicillin for strep throat (Study Days 324 thru 334);
- Oral Fluconazole 150-mg (indication: prevent yeast infection) (Study Days 334 and 335).

Subject CL-017 (b) (6) had a total of 11 TEAEs coded to the following PTs:

- Nausea x 2 (Study Days 21 to 22 and Study Days 103-106);
- Dizziness (Study Day 21);
- Blood Creatine phosphokinase x 2 (Study Days 103-106 and Study Days 187-208);
- Fungal infection NOS (Study Days 114 thru 116);
- Nasal Congestion (Study Days 135 to 137); PT: myalgias (Study Days 187 through 219);
- Bacterial vaginosis (Study Days 189 to 190);
- Smear Cervix abnormal (reported term: positive PAP high risk HPV) (Study Day 264 ongoing);
- Pharyngitis streptococcal (Study Day 323 thru 333).

Clinical Reviewer's Conclusions: For further discussion please refer to the subject narratives describing CPK elevations.

Subject CL-017- (b) (6) (Oteseconazole)

A 21-year-old White, Latino female with a past medical history only notable for a history of RVVC ([Table 177](#)). The subject received the first dose of study drug on Study Day 1 and received the final dose of study drug on Study Day 85.

This subject's sole concomitant medication was ethinyl estradiol/norgestimate (Sprintec) birth control pill (Study Day -658 – ongoing).

This subject was not reported to have had any TEAEs.

Clinical Reviewer's Conclusions: For further discussion please refer to the subject narratives describing CPK elevations.

Table 176. Results for Subject CL-017 (b) (6)

Results (Reference Range)	Baseline (D 1)	Day 14 (D 15)	Wk 8 (D 50/54)	Wk 14 (D 103/110 unsch)	Wk 20 (D 138)	Wk 26 (D 187/191)	Wk 32 (D 236)	Wk 38 (D 278)	Wk 44 (D 306/333)	Wk 50 (D 369/390)
ALT (≤33)	12	12	18/ 13 (unsch repeat)	49/ 21 (unsch repeat)	11	20 (100, unsch repeat)	9	40	6/10 (unsch repeat)	●/ 6 (unsch repeat)
AST (≤31)	17	18	20/18	187/22	16	60/284	14	29	14/19	●/ 16 (unsch repeat)
CPK (26-192)	134	155	145/145	8082/ (210 unsch)	95	3165/ (14833 unsch)	126	324	81/ (96 unsch)	●/ (88 unsch)
Cr (0.1-0.95)	0.6	0.71	0.97/0.62	0.91/ (0.69 unsch)	0.61	0.67/ (0.85 unsch)	0.9	0.73	0.73/ (0.73 unsch)	0.65/ (0.72 unsch)
Tbili (≤1.2)	0.3	0.5	0.6/0.6	0.5/0.6	0.7	0.4/1	0.6	0.8	●/(0.7, unsch repeat)	●/(0.4, unsch repeat)
Dbili (0-0.3)	0.1	0.1	0.2/0.2	0.1/0.2	0.2	0.2/0.2	0.2	0.2	●/ (0.1, unsch repeat)	●/ (0.1, unsch repeat)
Alk phos (35-104)	78	77	68/64	67/63	68	63/58	65	59	●/ (62, unsch repeat)	●/ (72, unsch repeat)

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

Table 177. Results for Subject CL-017 (b) (6)

Results (Reference Range)	Baseline (D 1)	Day 14 (D 15)	Wk 8 (D 55)	Wk 14 (D 90)	Wk 20 (D 131)	Wk 26 (D 170)	Wk 32 (D 215)	Wk 38 (D 279)	Wk 44 (D 309)	Wk 50 (D 343)
ALT (≤33)	12	11	12	11	11	13	12	14	12	91
AST (≤31)	20	18	18	16	18	17	17	22	18	173
Tbili (≤1.2)	0.3	0.8	0.5	0.3	0.7	0.3	0.3	0.4	0.4	0.6
Dbili (0-0.3)	0.1	0.2	0.1	0.1	0.2	0	0.1	0.1	0.1	0.1
Alk phos (35-104)	119	73	106	103	77	110	100	95	83	82

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

CL-006

Subject CL-006 (b) (6) (Oteseconazole 300-mg x24 Weeks)

A 26-year-old White, Latino female with a past medical history most notable for depression/anxiety/panic attacks (b) (6) a history of chlamydia (b) (6) and a history of bacterial vaginosis (b) (6) s/p Mirena IUD insertion (b) (6) and a history of RVVC (Table 176). The subject received the first dose of oteseconazole on Study Day 1 and the last dose of oteseconazole on Study Day 168.

Concomitant medications included:

- Mirena IUD
- Macrobid 100 mg twice daily (Study Days: 179-185) for UTI
- Topical Mycolog (nystatin/triamcinolone cream) twice daily for candida infection (Study Days: 171-196)
- Vitamin B12 500 g daily (Study Day 210 -ongoing)

Subject had a single nonserious TEAE (PT: UTI; Study Days 171-185). The Study Investigator determined this UTI to be unrelated to the study treatment.

***Clinical Reviewer's Conclusions:** For further discussion please refer to the subject narratives describing CPK elevations.*

Subject CL-006 (b) (6) (Oteseconazole 300-mg x12 Weeks)

A 27-year-old Asian, non-Latino female with a past medical history noted for depression (b) (6) (b) (6) heartburn (since (b) (6)); chronic urinary tract infections (b) (6) dysmenorrhea (since (b) (6)); intracyclic vaginal bleeding (since (b) (6)); and a history of RVVC (Table 179). The subject received the first dose of oteseconazole on Study Day 1. The final day of study drug treatment was on Study Day 168.

Concomitant medications included:

- Aspirin as needed for migraines (Study Day -1581 through ongoing);
- Aleve for knee pain (Study Days 20-26);
- Methylprednisolone oral tablets (Study Days 331-336);
- Dayquil (acetaminophen-dextromethorphan and phenylephrine) (Study Days 201-204);
- Mucinex (Study Days 313-314);
- Nyquil (acetaminophen-dextromethorphan and doxylamine succinate) (Study Days 201 – 204) all for an upper respiratory tract infection.

Other concomitant medications included: Tums for heartburn (Study Day -3407 ongoing), ON essential amino energy pre workout supplement (health supplement) (Study Days -61 ongoing), and Gaia Diet Slim Herbal Tea (health supplement) (Study Days -212 ongoing).

This subject had two reported TEAEs coded to arthralgias (Study Days 14 - 26) and upper respiratory tract infections, x 2 (Study Days 201-206; Study Days 311 -336). Neither of which was deemed related to oteseconazole or met criteria for an SAE.

NDA 215888
Vivjoa (oteseconazole)

Subject CL-006 (b) (6) (Oteseconazole 300-mg x12 Weeks)

A 26-year-old White, non-Latino female with a past medical history most notable for GERD (since (b) (6)); seasonal allergies (b) (6) cervical disc disease (since (b) (6)); and a history of RVVC ([Table 180](#)). The subject received the first dose of oteseconazole on Study Day 1 and received the final day of oteseconazole exposure was on Study Day 162.

Concomitant medications included:

- Benadryl (antihistamine) (Study Days 23 -25) for rash on legs and stomach
- Dayquil cold and flu as needed (Study Days 165 and 169)
- Nyquil cold and Flu as needed (Study Days 167 and 169)
- Condoms with spermicide as needed (Study Days -1980 ongoing)

The subject experienced **two nonserious TEAEs** coded to the following PTs:

- Rash (Study Days 23-25)
- Nasopharyngitis (Study Days 165 and 169)

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Table 178. Results for Subject CL-006 (b) (6)

Results (Reference Range)	Screening (D -14)	Baseline (D 1)	Day 7 (D 10)	Wk 4 (D 31)	Wk 8 (D 58/64, unsch)	Wk 12 (D 78 unsch/88)	Wk 18 (D 122)	Wk 24 (D 171)	Wk 36 (D 241)	Wk 48 (D 331)
ALT (≤33)	16	16	16	13	108/ (71 unsch)	18 (unsch) /12	11	21	21	25
AST (14-34)	23	25	27	17	515/ (66 unsch)	(22 unsch) /19	16	21	25	25
Tbili (≤1.2)	0.4	0.8	0.6	0.6	0.6/ (0.5)	(0.7 unsch) /(0.7)	0.4	1.0	0.6	0.5
Dbili (0-0.3)	0.1	0.2	0.2	0.2	0.2/(0.1 unsch)	(0.2 unsch) / 0.2	0.1	0.3	0.2	0.2
Alk phos (42-98)	55	57	55	54	57/(49 unsch)	(54 unsch)/ 53	54	60	64	67

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

Table 179. Results for Subject CL-006 (b) (6)

Results (Reference Range)	Screening (D -15)	Baseline (D 1)	Day 7 (D 7)	Wk 4 (D 28)	Wk 8 (D 56)	Wk 12 (D 85)	Wk 18 (D 123)	Wk 24 (D 158/ 166)	Wk 36 (D 249/ 256, unsch)	Wk 48 (D 298/340)
ALT (≤33)	13	12	23	15	12	8	13	13/15	36/ (86, unsch)	(19, unsche) /19
AST (14-34)	21	24	33	24	21	18	21	27/21	86/ (179, unsch)	(25 unsch)/24
Tbili (0.3-1.2)	0.8	0.6	0.9	0.9	1.0	1.0	0.7	0.8/ (0.7, unsch)	0.7 (0.8 unsch)	(0.8 unsch)/ (0.4)
Dbili (0-0.3)	0.2	0.2	0.3	0.2	0.3	0.3	0.2	0.2/ (0.2 unsch)	0.2/ (0.3 unsch)	(0.3 unsch) / 0.1
Alk phos (42-98)	74	67	72	67	64	56	53	60/ (63 unsch)	62/ (50 unsch)	57/ (57 unsch)

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

NDA 215888

Vivjoa (oteseconazole)

Table 180. Results for Subject CL-006 (b) (6)

Results (Reference Range)	Screening (D -16)	Baseline (D 1)	Day 7 (D 9)	Wk 4 (D 29/37 unsch.)	Wk 8 (D 57)	Wk 12 (D 85)	Wk 18 (D 127)	Wk 24 (D 167)	Wk 36 (D 259)	Wk 48 (D 323)
ALT (≤ 33)	25	72	77	262/109	69	76	42	20	15	10
AST (14-34)	27	79	57	152/ (59, unsch)	63	69	37	25	25	15
Tbili (0.3-1.2)	0.2	0.3	0.2	0.4/ (0.3 unsch)	0.4	0.3	0.4	0.2	0.5	0.2
Dbili (0-0.3)	0.1	0.2	0.1	0.1/ (0.1 unsch)	0.1	0.1	0.1	0.1	0.1	<0.1
Alk phos (42-98)	87	97	101	122/ (98 unsch)	104	109	98	86	84	76

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

17.3.2. Medical Dictionary for Regulatory Activities- Based Adverse Event Diagnostics Related Hepatic Function Elevations Narratives

Trial CL-011

Subject CL-011 (b) (6) (Oteseconazole) (PT: ALT Increased and AST Increased)

A 35-year-old Asian, non-Latino Japanese, female with a past medical history most notable for prior chlamydial infection (b) (6), genital herpes (b) (6) seasonal allergy (b) (6) and a history of RVVC (Table 179). The subject received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole on Study Day 85. Subject (b) (6) sustained the following key non-SAE TEAEs:

- Facial spasm (Study Day 11) treated with concomitant medications ambroxol HCL (Study Days 15 to 19), benfotiamine (vitamin B1-cyanocobalamin-pyridoxine HCL (Study Days 15 to 52), and clonazepam (Study Days 15-19);
- Nasopharyngitis (Study Day 56) treated with concomitant medication Pabron (Study Day 56);
- ALT increased (Study Day 108 to 134);
- AST increased (Study Day 108 to 134);
- Genital herpes, worsening treated with concomitant medication valacyclovir on Study Days 226-309;
- Abdominal pain lower (Study Day 284).

Other on treatment medication was famotidine (Study Day 15-19) for gastritis prevention.

Pre-treatment concomitant medications included: Bifidobacterium nos (probiotic), citrus reticulata peel (oil), berberine tannate all for feces, epinastine HCL for rhinitis, ethinylestradiol-levonorgestrel contraceptive pill, valacyclovir (pre-treatment through Study Day 21), bepotastine for pollinosis.

Subject CL-011 (b) (6) (Oteseconazole) (PT: ALT Increased and AST Increased)

A 40-year-old White, non-Latino Polish female with a past medical history most notable for depression (b) (6) hypothyroidism (b) (6) s/p laparotomy (b) (6) and a history of RVVC (Table 182). The subject received the first dose of oteseconazole on Study Day 1. The final dose of oteseconazole was received on Study Day 84. Subject (b) (6) was reported have the following non-SAE TEAE: ALT increased (Study Day 1-42), AST increased (Study Days 1-14), (PT: cystitis x 2; Study Days 3 and 86) treated with concomitant medication akritoin (Study Days 3-9 and Study Days 86-90) for a “bladder infection.”

Pre-treatment concomitant medications included:

- Desogestrel-ethinylestradiol (Mercilon) hormonal contraceptive pills;
- Levothyroxine for hypothyroidism;
- Bupropion for depression;
- Gynoflor (lactobacillus acidophilus + estriolum);
- Clotrimazole for “vaginal infection.”

Subject CL-011 (b) (6) (Oteseconazole) (PT: Transaminases Increased/Blood Creatine Phosphokinase Increased)

A 38-year-old White, non-Latino female with a past medical history most notable for a history of atypical squamous cell of undetermined significance on Pap smear related to HPV infection (b) (6); a history of UTI (b) (6) back pain (b) (6) and a history of RVVC (Table 183). The subject received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole on Study Day 85.

Subject CL-011 (b) (6) reportedly had non-SAE TEAE including: transaminases increased (Study Day 1-13), Blood creatine phosphokinase increased (Study Day 1); and upper respiratory tract infection (Study Day 148) treated with several concomitant medications including:

- Vicks nasal spray (Study Days 149-159);
- Sudafed (pseudoephedrine) (Study Days 149-154);
- Mucinex (guaifenesin) (Study Days 155-157);
- Allegra (fexofenadine) (Study Days 159-184) among others.

Pre-treatment concomitant medications included: multivitamin (health supplement), Azo vaginal health (lactobacillus) as prophylaxis, and drospirenone (Loesterin) (oral contraceptive pill).

Clinical Reviewer's Conclusions: For further discussion please refer to the subject narratives describing CPK elevations.

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Table 181. Results from Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -12)	Baseline (D 1)	Day 14 (D 16)	Wk 6							
				(D 45/74 unsch.)	Wk 12 (D 85/108)	Wk 18 (D 134)	Wk 24 (D 171)	Wk 30 (D 211)	Wk 36 (D 248)	Wk 42 (D 298)	Wk 48 (D 323)
ALT (≤33)	20	25	14	19/22	21/57	26	19	14	24	28	14
AST (14-34)	21	23	16	19/22	20/48	23	18	16	20	20	13
Tbili (0.3-1.2)	0.4	0.4	0.2	0.2/0.2	0.2/0.2	0.3	0.2	0.2	0.2	0.3	0.4
Dbili (0-0.3)	0.2	0.1	0.1	0.1/0.1	●/0.1, unsch	0.1	●	0.1	0.1	0.1	0.1
Alk phos (42-98)	47	51	43	46/50	53/47	57	59	51	56	45	49

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

Table 182. Results from Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -13, -5 unsch)	Baseline (D 1)	Day 14 (D 14)	Wk 6 (D 42)	Wk 12 (D 86)	Wk 18 (D 129)	Wk 24 (D 168)	Wk 30 (D 216)	Wk 36 (D 252)	Wk 42 (D 300)	Wk 48 (D 350)
ALT (≤33)	70/55	90	55	21	16	9	14	10	11	9	11
AST (14-34)	35/31	47	28	19	19	13	18	15	19	16	16
Tbili (0.3-1.2)	0.3/0.3	0.3	0.4	0.2	0.3	0.2	0.3	0.3	0.2	0.3	0.2
Dbili (0-0.3)	0.1/0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Alk phos (42-98)	58/67 unsch	70	55	57	59	63	63	49	55	65	56

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

Table 183. Results from Subject CL-011 (b) (6)

Results (Reference Range)	Screening (D -14)	Baseline (D 1)	Day 14 (D 13)	Wk 6 (D 42)	Wk 12 (D 92)	Wk 18 (D 147)	Wk 24 (D 168)	Wk 30 (D 209)	Wk 36 (D 252)	Wk 42 (D 292)	Wk 48 (D 350)
ALT (≤33)	18	49	17	21	17	18	16	15	14	19	22
AST (14-34)	19	44	18	20	20	23	22	15	16	18	23
Tbili (0.3-1.2)	0.7	0.4	0.5	0.5	0.6	0.7	0.5	0.4	0.6	0.5	0.7
Dbili (0-0.3)	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Alk phos (42-98)	39	35	35	33	35	33	38	39	37	37	40

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

Medical Dictionary for Regulatory Activities -Based Adverse Event Diagnostics—Trial CL-012

Subject CL-012 (b) (6) (Oteseconazole) (PT: Hepatitis)

A 54-year-old White, non-Latino, Romanian female with a past medical history most notable for hypertension (b) (6) obesity (BMI 31.9) (b) (6) and a history of RVVC (Table 184). The subject received the first dose of oteseconazole on Study Day 1 and the final dose of oteseconazole on Study Day 86.

Subject (b) (6) sustained the non-SAE TEAE hepatitis (Study Day 95-99) and cholecystitis infective (Study Day 94-99) which was treated with the following concomitant medications:

- IV ampicillin (Study Day 95);
- Ceftriaxone (Study Day 95-97);
- Dexketoprofen (a nonsteroidal anti-inflammatory) (Study Day 95-96);
- IV drotaverine (an antispasmodic) (Study Day 95);
- Famotidine (Study Day 95-98);
- IV fempiverinium (an antispasmodic and anticholinergic) (Study Day 95-98);
- Intramuscular gentamicin (Study Day 95-97);
- Metamizole (a painkiller, antispasmodic) (Study Day 95);
- Metronidazole (Study Day 95-96); and
- Nadroparin (a low molecular weight heparin) (Study Day 95-98).

Pre-treatment concomitant medications included sotalol reportedly for arterial hypertension.

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Table 184. Results From Subject CL-012 (b) (6)

Results (Reference Range)	Screening (D -14)	Baseline (D 1)	Day 14 (D 16)	Wk 6 (D 46)	Wk 12 (D 80)	Wk 18 (D 134/154 unsch)	Wk 24 (D 177)	Wk 30 (D 206)	Wk 36 (D 246)	Wk 42 (D 296)	Wk 48 (D 350)
ALT ($\leq$ 33)	15	32	13	15	14	●/14	22	18	24	●	●
AST (14-34)	18	25	16	16	15	●/16	19	19	24	●	●
Tbili (0.3-1.2)	0.5	0.5	0.4	0.5	0.3	0.5/0.3	0.6	0.4	0.5	0.5	●
Dbili (0-0.3)	0.2	0.1	0.1	0.1	0.1	●/0.1	0.2	0.1	0.2	●	●
Alk phos (35-104)	83	86	86	97	87	98/99	109	110	36	100	●

Source: Reviewer generated table based on data from ADLB data set.

Abbreviations: Alk phos; a kaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, study day; Dbili, direct bilirubin; T bili, total bilirubin; wk, week.

17.3.3. Drug Allergy/Hypersensitivity/Anaphylactic Reactions

The reviewer identified several PTs potentially suggestive of hypersensitivity reactions in the phase 3 integrated summary of safety (ISS) database. There were no reported cases of anaphylaxis. Narratives of these reported cases are described below.

Subject CL-012 (b) (6) (Oteseconazole) (PT: Drug Hypersensitivity)

A 54-year-old White, non-Latino female who experienced 4 events each coded to drug hypersensitivity (Study Days 51, 57, 76, and 77). Events were described as self-limited and did not require the subject to change or discontinue study treatment. No additional actions were taken. The investigator determined that the event was related to the study drug. Other concomitant medications potentially implicated in the finding were ibuprofen and Furodontine (nitrofurantoin).

Relevant concomitant medications:

- Omeprazole (Study Days -7305 – ongoing);
- Estradiol (Study Days -474 – ongoing);
- Progesterone (Study Days -474- ongoing);
- Levothyroxine (Study Days -85 – ongoing);
- Ibuprofen (Study Days 8-77);
- Nitrofurantoin (Study Day 51 and 57)

Clinical Reviewer's Comments: The other listed concomitant drugs are potential confounders. Onset of a delayed hypersensitivity reaction occurring approximately 2 months into oteseconazole treatment makes causality between oteseconazole and the observed event unlikely although the possibility cannot be excluded.

Subject CL-017 (b) (6) (Oteseconazole) (PT: Dermatitis, Swelling)

A 34-year-old White, non-Latino female received the first dose of oteseconazole treatment on Study Day 1. Last dose was received on Study Day 85. On Study Days 77 - 98 and 99-213, respectively, the subject was reported to have developed dermatitis and swelling. Each event was assessed as a Grade 2 event and were described as self-resolving. Neither event was determined to be related to oteseconazole nor were identified as SAEs. The subject completed study participation on Study Day 350.

Relevant concomitant medications:

- Albuterol nebulizer (Study Days -1301 – ongoing);
- Doxepin (Study Days -1301 – ongoing);
- Flovent HFA (Study Days -167-67; 98 -ongoing);
- Prednisone (Study Days 91-99);
- Mometasone (Study Days 98-213);
- Furosemide (Study Days 126-140; 164-ongoing);
- Fluconazole (Study Day 140; 224; 302-330; 331-ongoing);
- Brompheniramine-dextromethorphan-pseudoephedrine (Study Days 140-147);

NDA 215888
Vivjoa (oteseconazole)

- Ketoconazole cream (Study Days 213-224);
- Topical nystatin/triamcinolone (Study Day 331-ongoing)

Clinical Reviewer's Comments: *Details are too limited to make a definite determination on the observed findings. Although there is overlap between drug exposure and the first (PT: dermatitis), the event occurred 77 days post the start of treatment and hence is unlikely to be a result of oteseconazole.*

Subject CL-017 (b) (6) (Oteseconazole) (PTs: Dermatitis Allergic)

A 38-year-old White, non-Latino female received the first dose of oteseconazole on Study Day 1. That same day, the subject reportedly developed a “diffuse allergic eruption with an erythematous macular rash” and was withdrawn from study treatment. The event was not an SAE and was assessed as a Grade 3 event. The subject recovered from the event. The Investigator assessed the event to be related to oteseconazole administration. The subject recovered from the event.

Concomitant medications:

- IV diphenhydramine (Study Day 1 and 2);
- IV ondansetron (Study Day 1);
- IV sodium chloride (Study Day 1); dexamethasone IV (Study Day 2);
- IV famotidine (Study Day 2);
- Oral famotidine (Study Days 3-9);
- Oral hydroxyzine (Study Days 3-12);
- Oral methylprednisone (Study Days 3-8)

Clinical Reviewer's Comments: *The event had a rapid onset of action and is very likely causally related to oteseconazole administration. The event was described in greater detail in Section [17.2](#) under TEAEs Leading to Discontinuation of Study Drug.*

Subject CL-017 (b) (6) (Oteseconazole) (PT: Dermatitis Contact)

A 31-year-old White, Latino female randomized to oteseconazole. On Study Days 2 to 9, subject experienced dermatitis contact. No actions were taken. The event was evaluated as a Grade 1 event and was reportedly self-resolving. The Study Investigator assessed the event as being related to oteseconazole exposure.

Concomitant medications:

- Ethinyl estradiol/ norgestimate (Ortho Tricyclen, birth control) (Study Days -637 to 93; Study Day 158 - ongoing);
- Probiotics nos (Study Day -272 – ongoing);
- Oseltamivir (Tamiflu) (Study Days 85-90);
- Doxycycline (Study Days 189 -ongoing);
- Spironolactone (Study Days 189- ongoing)

Other PT:

- Influenza (Study Days 83-97);
- Acne cystic (Study Days 144-235);
- Blood creatine phosphokinase (Study Days 153-179)

***Clinical Reviewer's Comments:** Given the temporal association between oteseconazole administration and the onset of the event, the reviewer believes that the described event was related to oteseconazole administration.*

Subject CL-017 (b) (6) (Oteseconazole) (PT: Urticaria)

A 26-year-old White, non-Latino female who was randomized to oteseconazole. The described event was a Grade 3, nonserious TEAE. Subject received the first dose of oteseconazole on Study Day 1. On Study Days 3 through 9, the subject developed urticaria that was ongoing at the time of reporting. The dose of oteseconazole was reportedly not changed. The subject was begun on a new drug, presumably for the event. The final exposure to study drug was on Study Day 7. The subject ended participation in the study on Study Day 9. The Investigator assessed the event as being related to oteseconazole.

Concomitant Medications:

- Insulin glargine (Lantus) (Study Days -4748 – ongoing);
- Insulin lispro (Study Days -4748 – ongoing);
- Diphenhydramine hydrochloride (Study Days 7 – ongoing);
- Triamcinolone (Study Days 7 – ongoing);
- Methylprednisolone (Medrol pack) (Study Days 10- ongoing);
- Macrobid (nitrofurantoin) (Study Days 13 – ongoing)

***Clinical Reviewer's Comments:** Given the temporal association between oteseconazole administration and the onset of the event, the reviewer agrees that the described event was related to oteseconazole administration.*

Subject CL-017 (b) (6) (Oteseconazole) (PT: Dermatitis Contact)

A 33-year-old White, non-Latino female randomized to oteseconazole. The subject's first day of oteseconazole exposure was on Study Day 1 and the final day of exposure was on Study Day 85. On Study Days 26 -35 and Study Days 138 -165, the subject experienced two events both coded to dermatitis contact due to poison ivy exposure. Subject developed a rash on both occasions. The events were listed as a non-SAE, treatment-emergent AEs that were eventually resolved. Oteseconazole dosing was not changed due to the event and no additional actions were taken. The event was assessed as a Grade 1 event. On both occasions the Study Investigator assessed the events as being unrelated to oteseconazole exposure. The subject continued participation in the study until completing the study on Study Day 349.

Other PTs:

- Rash (Study Day 11-22);
- Cellulitis (Study Days 53-97)

Concomitant Medications:

- Cefalexin (Keflex) (Study Days 63-69; Study Days 90-97) for cellulitis

Clinical Reviewer's Comments: *The subject has a clear alternative explanation (poison ivy exposure) to account for the observed TEAEs. The author agrees that the reported AEs were unrelated to oteseconazole exposure.*

Subject CL-012 (b) (6) **(Oteseconazole) (PT: Rash Generalized)**

A 24-year-old White, non-Latino female randomized to oteseconazole. The subject began oteseconazole on Study Day 1 and received final dose of oteseconazole on Study Day 85. On Study Days 40 - 235, the subject was reported to develop a generalized rash which did not require subject to withdraw from oteseconazole. This non-SAE, TEAEs was described as resolved at the time of final reporting. Oteseconazole dosing was not changed due to the reported TEAE. A new drug therapy was added. The event was evaluated as a Grade 1 toxicity event and was reported as being unrelated to oteseconazole administration.

Concomitant medications:

- Duloxetine for anxiety (Study Days -405 - ongoing);
- Subcutaneous etonogestrel, birth control (Study Days -279- ongoing);
- Oral prednisone for generalized rash (Study Days 40-42; 43-45);
- Intramuscular triamcinolone for generalized rash (Study Day 43);
- Oral prednisone for generalized rash (Study Days 46-48; 49-51);
- Phentermine for weight gain (Study Days 85-314);
- Fluconazole for vaginitis (Study Days 235);

Post event concomitant medications included: amoxicillin for urinary tract infection (Study Days 237-243), topiramate for worsening depression (Study Day 297- ongoing), and hydroxyzine for worsening depression (Study Days 298 – ongoing).

Clinical Reviewer's Comments: *While the reported TEAE initially appeared to be related to oteseconazole since it occurred during active receipt of the drug, the reviewer believes that subject's rash was unrelated to the study drug due to its late onset, Study Day 40, and because the rash persisted long after the subject had completed the study (although oteseconazole is noted to have a prolonged half-life).*

Subject CL-012 (b) (6) **(Oteseconazole) (PT: Dermatitis)**

A 30-year-old Black/African-American, non-Latino female randomized to oteseconazole. The subject received first dose of oteseconazole on Study Day 1 and received the final dose of oteseconazole on Study Day 85. Shortly before completing the on-treatment portion of the study and shortly afterwards, the subject developed a non-SAE, Grade 1 TEAE coded to dermatitis (reported term: dermatitis on back of left leg) (Study Days 80 - 94). The subject was reported to have recovered from the event. The subject did not require any dose changes to oteseconazole and no additional actions were taken. The Study Investigator determined that the event was unrelated to oteseconazole treatment. The subject was able to complete participation in the study on Study Day 337.

Relevant concomitant medications:

- Dextroamphetamine-amphetamine for attention-deficit/hyperactivity disorder (Study Day -29 – ongoing);
- Sertraline (Zoloft) (Study Day 147 – ongoing).

Clinical Reviewer's Comments: *There is limited available information to assist in fully adjudicating causality for this case. However, there is a temporal association between the event onset and oteseconazole exposure, which precludes this reviewer from excluding the possibility that there is possible causal relationship between the TEAE and oteseconazole exposure. The reviewer acknowledges that a late onset allergic reaction, occurring approximately 3 months after initiation of oteseconazole, is very unlikely.*

Subject CL-11 ^{(b) (6)} **(Oteseconazole) (PT: Urticaria x2)**

A 34-year-old Japanese, non-Latino female who was randomized to receive oteseconazole. Subject received the first dose of oteseconazole on Study Day 1 and received the final dose on Study Day 85. The subject experienced 2 TEAEs coded to urticaria on Study Days 166-177 and 297-337. Upon completion of oteseconazole prophylaxis, subject developed a Grade 1, non-SAE, TEAE coded to urticaria. No changes were made to oteseconazole dosing during either episode since oteseconazole exposure had ended. New medications were required to address the TEAEs. The Study Investigator determined that neither event was related to oteseconazole exposure.

Relevant concomitant medications: Concomitant medications at or around the reported TEAE included:

- Paracetamol for migraine (Study Days 730 – 146; 157-ongoing);
- Sulpiride for GERD (Study 80 – ongoing);
- Ethinyl estradiol/norgestrel (Study Days 6 – ongoing);
- Neticonazole cream for RVVC (Study Days 19 – ongoing);
- Cromoglicate for pollinosis (Study Days 148-225);
- Bilastine (Study Days 163-168; Study Days 171-176 for urticaria; Study Days 133-313 for pollinosis);
- Dexchlorpheniramine maleate for urticaria (Study Days 169-170);
- Rupatadine fumarate for urticaria (Study Days 169);
- Betamethasone-dexchlorpheniramine maleate for urticaria (Study Days 170-176);
- Hydrocortisone for urticaria (Study Day 170, 304, 308);
- Ethyl loflazepate for adjustment disorder (Study Days 23-206; 215-327; 328-ongoing);
- Betamethasone for urticaria (Study Days 304-308);
- Dexchlorpheniramine for urticaria (Study Day 304, 308);
- Hydrocortisone for urticaria (Study Day 304, 308);
- Diphenhydramine for urticaria (Study Days 308-ongoing);
- Levocetirizine dihydrochloride (Study Days 314-ongoing);

Clinical Reviewer's Comments: *The reviewer is in agreement with the Study Investigator, that both events occurred outside of the on-treatment time period in which a true dermatologic allergy would have occurred.*

Subject CL-11 (b) (6) 5 (Oteseconazole) (PT: Urticaria)

A 34-year-old non-Latino, Japanese woman who was randomized to receive oteseconazole. The subject received the first dose of oteseconazole on Study Day 1 and received the final dose on Study Day 85. On Study Days 15-66, subject developed a Grade 1, non-SAE, TEAE coded to urticaria that required no changes to oteseconazole dosing but did require the addition of a new drug treatment. Subject recovered from the TEAE approximately 52 days after event onset. The Study Investigator assessed the event as being unrelated to oteseconazole exposure.

Key concomitant medications:

- Famotidine (Study Day 12-13)
- Paracetamol (Study Day 12-13)
- Difluprednate (Study Days 15-65)
- Levocetirizine (Study Days 15-29)
- Rupatadine dihydrochloride (Study Days 36-55)

***Clinical Reviewer's Comments:** While the observed PT occurred early during oteseconazole treatment, the urticaria was not reported to worsen and the participant was able to complete the treatment regimen. The reviewer cannot exclude the possibility that the event may be causally related to oteseconazole dosing given the timing of the event. However, the subject being able to complete treatment made it less likely that the event was related to oteseconazole or otherwise the staff was able to successfully treat urticaria with the appropriate therapeutic agents.*

Subject CL-11 (b) (6) (Oteseconazole) (PT: Urticaria)

A 31-year-old non-Latino, Japanese female randomized to receive oteseconazole. Subject received the first dose of oteseconazole on Study Day 1 and received the final dose on Study Day 86. On Study Days 34 and 54, subject experienced a Grade 1 non-SAE, TEAE coded to urticaria which required the addition of a new drug therapy but ultimately from which the subject recovered. No change to oteseconazole dosing was required and the subject completed oteseconazole treatment. The Investigator determined that the TEAE was unrelated to the study drug.

Key concomitant medications: Concomitant medications at or around the reported TEAE included:

- Levonorgestrel intravaginal contraceptive (Study Days -845 – ongoing);
- Rebamipide for prophylaxis of ulcers/gastritis (Study Days -730- ongoing; 16-21);
- Tranexamic acid for common cold (Study Days 16-21);
- Valerate- for urticaria (Study Dyas 44 -53);
- Bilastine (Study Days 44-53);
- Montelukast sodium for bronchitis (Study Days 44-53)

***Clinical Reviewer's Assessments:** The subject experienced urticaria approximately half-way through oteseconazole treatment. While the observed PT occurred on treatment, there is no indication that the urticaria worsened with continued oteseconazole exposure hence making the likelihood that the TEAE was induced by oteseconazole less likely, but not impossible that there is some relationship between to oteseconazole. However, the reviewer agrees that the event is most likely unrelated to oteseconazole dosing.*

Subject CL-12 (b) (6) **(Oteseconazole) (PT: Blister)**

A 25-year-old White, non-Latino Romanian female was randomized to the oteseconazole. The reader is referred to the discussion of TEAEs leading to study drug discontinuation for further details on this subject who sustained a Grade 2, non-SAE, treatment-emergent AE that resulted in withdrawal from study. The subject received first dose of oteseconazole on Study Day 1 and received final dose of oteseconazole on Study Day 7.

Concomitant medications: none documented

Clinical Reviewer's Assessment: Please refer to Section [17.2](#) of the review for the discussion on TEAEs leading to study drug withdrawal.

Subject CL-11 (b) (6) **(Oteseconazole) (PT: Urticaria)**

A 56-year-old Black/African-American, Latino female was randomized to receive oteseconazole. The subject received the first dose of oteseconazole on (b) (6) and received the final dose on Study Day 86. The subject completed participation in the study on Study Day 323.

On Study Day 193, post-oteseconazole therapy, the subject experienced a non-SAE, AE Grade 1 event coded to urticaria (reported term: hives) (Study Day 193-202). This event required no changes to oteseconazole dosing (which had been completed at the time of the event), resulted in a complete recovery of the event, and required that subject begin a new medication. The Investigator assessed the observed event as being unrelated to the study drug.

Key concomitant medications: Concomitant medications at or around the reported TEAE included:

- Levocetirizine dihydrochloride for allergic rhinitis (-4748 -ongoing);
- RepHresh and vitamin D nos as health maintenance (Study Days to ongoing); and
- Methylprednisolone for hives (Study Days 197-202).

Clinical Reviewer Assessment: The author notes that it would be unlikely for an allergic reaction/urticaria to occur outside of the acute setting. The discussed event occurred when the subject was no longer receiving oteseconazole (approximately 108 days post-treatment) and therefore makes attribution of the TEAE with oteseconazole unlikely. The clinical reviewer agrees with the Investigator that the event was unrelated to oteseconazole.

Subject CL-011 (b) (6) **(Oteseconazole) (PT: Dermatitis Contact)**

A 29-year-old White, non-Latino female was randomized to receive oteseconazole. Subject received first dose of oteseconazole on Study Day 1 and received final dose of oteseconazole on Study Day 78. On Study Days 10 – 19, subject experienced a Grade 1 nonserious, treatment-emergent AE, dermatitis contact, that did not require a change to oteseconazole dosing but did require addition of a new drug therapy. The subject recovered from the event completed the treatment regimen and remained in the study through study completion on Study Day 339. The Study Investigator assessed the event was as being unrelated to the study drug.

Key concomitant medications: Concomitant medications at or around the reported TEAE included:

- Multivitamins/health supplement (Study Days -3652 – ongoing);

- Valacyclovir for herpes (Study Days -1826 -ongoing);
- Phentermine for weight management (Study Day 1 -ongoing);
- Diphenhydramine for contact dermatitis (Study Days 10-94);
- Spironolactone (Study Days 101 – ongoing)

Clinical Reviewer's Assessment: *Despite the limitations of the available information, it is reassuring that the subject experienced a recovery from the described TEAE while remaining on oteseconazole therapy. Given the temporal relatedness between treatment onset and the emergence of the above-described TEAE, the reviewer cannot exclude the possibility that the event may be attributable to oteseconazole exposure. It appears that symptoms were managed with the use of the concomitant medication diphenhydramine*

Subject CL-012 (b) (6) (Oteseconazole) (PT: Dermatitis)

A 23-year-old White, Latino female was randomized to receive oteseconazole. Subject received the first dose of oteseconazole on Study Day 1 and received the final dose of oteseconazole on Study Day 83. Subject was observed to develop a pre-treatment Grade 2 AE coded to PT: dermatitis on Study Day -5 through 6 which given its pre-treatment onset was deemed unrelated to oteseconazole. The subject was able to receive oteseconazole with no need for dose changes and subject was noted to recover from the event on day 6 of oteseconazole exposure.

Concomitant medications:

- Oral folic acid (vitamin supplement) (Study Days -1095 – ongoing)
- Oral vitamin B12 (vitamin supplement) (Study Days -1095 – ongoing)
- Topical hydrocortisone for retro-auricular dermatitis (Study Days -1 – 14) ongoing)
- Dextromethorphan for common cold (Study Days 254 – 263)
- Paracetamol for common cold (Study Days 254 – 263)
- Oral Phenylephrine for common cold (Study Days 254 – 263)

Clinical Reviewer's Assessment: *The above-described event was a nontreatment-emergent adverse event. Since the described event occurred prior to receipt of oteseconazole, and the event did not appear to worsen while subject was on oteseconazole, the reviewer agrees with the Study Investigator that this nontreatment-emergent event is unrelated to oteseconazole.*

17.4. Creatine Phosphokinase Narratives

17.4.1. CPK Elevations-Trial CL-011

Subject (b) (6)

Grade 4 CPK Elevations $\geq 20 \times$ ULN Study Day 45 of Oteseconazole Treatment

A 50-year-old Black/African-American, non-Latino female with a prior medical history relevant for genital herpes for which the sole concomitant medication was valacyclovir as needed. Subject was observed to have a baseline CPK of 166 U/L (within normal limits [wnl]). On Study Day 45 of oteseconazole (OTE) treatment, the subject was observed to have a **Grade 4 CPK elevation** of 11,188 U/L (58x upper limit of normal [ULN]). This finding was associated with **Grade 3 AST elevations** (AST of 142 U/L, 4.6x ULN) and **Grade 1 ALT elevations** (ALT of 65 U/L,

2.0x ULN) which were also witnessed to occur on Study Day 45. Study Day 45 creatinine (Cr) levels and subsequent Cr levels were unaffected by the reported CPK elevation, as were pre- and post- potassium (K⁺), phosphate, and calcium (Ca²⁺) levels. This event was the subject's sole reported TEAE (PT: blood creatine phosphokinase increased Study Day 45-56). The Study Investigator and Applicant believed this event to be unrelated to the study drug. The dose of oteseconazole was not changed and no further actions were taken. The patient completed study.

Clinical Reviewer: *The observed CPK elevation lasted approximately 12 days (Study Day 45 - Study Day 56) and was temporally associated with on treatment oteseconazole exposure, although it did not require discontinuation of oteseconazole. There were no reported related TEAEs such as myopathy, muscle pain or weakness associated with the observed CPK elevations.*

Probably related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life and the temporal relatedness of the event to drug administration, the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in other azoles—itraconazole in the post-market setting and voriconazole in <2% of cases. A causal mechanism of action between the drug and the observed event has not been elucidated.*

Subject (b) (6)

Grade 4 CPK Elevations $\geq$ 20 x ULN, Study Day 140 (1.8 Months Post-OTE Exposure)

A 33-year-old White, non-Latino female with no relevant past medical history was begun on oteseconazole on Study Day 1, with a baseline CPK value of 67 U/L (wnl; Grade 0). Final on-treatment CPK value (Study Day 88) was also within normal limits at 76 U/L. On Study Day 140, 53 days (1.8 months) after the end of treatment, the subject developed a transient **Grade 4** CPK elevation of 4166 U/L (21.7x ULN) (which spontaneously declined to 133 U/L on Study Day 151. Concomitant medications were all pre-treatment, including: cholestyramine (for diarrhea), multivitamins, and levonorgestrel oral contraceptive pill, and were unlikely culprits in the observed elevations. Subject's only TEAE (PT nausea) occurred on Study Days 3-5 of treatment. Coinciding with subject's Study Day 140 CPK elevations were a **Grade 2** AST elevation of 62 U/L (2x ULN) and a **Grade 1** ALT elevation of 46 U/L (1.4x ULN), both of which returned to baseline and pre-baseline levels shortly afterwards on Study Day 151 (AST of 13 U/L, ALT of 13 U/L), similar to what was observed with CPK elevations. Other related laboratories (e.g., Cr, K⁺, phosphate, Ca²⁺), pre-and post-event values remained within normal limits.

Clinical Reviewer: *Transient temporal association not requiring study drug discontinuation. This event was not captured by the Study Investigator as a TEAE event. The Applicant reported being fairly confident that the observed CPK elevation was unrelated to oteseconazole treatment since the event was transient in nature. The Applicant provided no alternative explanations for the observed CPK findings (e.g., strenuous exercise). The participant had no documented associated TEAEs of myopathy, muscle pain, muscle weakness.*

Probably related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, with the event occurring within the timeframe of the drug's first half-life (although the subject was no longer actively receiving the study drug), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.*

Subject (b) (6)

Grade 4 CPK Elevations $\geq 20 \times$ ULN, Study Day 202 (3.9 Months Post-OTE Exposure)

A 38-year-old Asian, non-Latino female with no pertinent medical history (e.g., multiple episodes of bacterial vaginosis, seasonal allergies) had a baseline (Study Day 1) CPK value of 136 U/L (wnl). Final on-treatment CPK value was 100 (wnl) (Study Day 85). On Study Day 202, 118 days (3.9 months) post-treatment, the subject was reported to have a **Grade 4** CPK elevation of 4140 (21.5xULN). Subsequent Study Day 221, 252, and 287 CPK values were within normal limits (wnl), with values of 81, 101, and 97, respectively. Simultaneous Study Day 202 laboratory elevations included **Grade 3** AST (96 U/L, 3.1x ULN) and **Grade 1** ALT elevations (39, 1.2xULN). These laboratory elevations were also transient and returned to baseline values on subsequent study days. Other pertinent laboratories, Cr, K⁺, phosphate, and Ca²⁺, remained within normal limits pre- and post- baseline and were unaffected by the observed CPK elevations.

The concomitant medication administered around the time of the CPK elevations was the third generation cephalosporin cefcapene for (PT: cystitis) (Study Days 202 to 205). Simultaneous TEAEs occurring at or around the time of the witnessed CPK elevations included: (PT: blood triglycerides) (Study Days 177 to 183); (PT: cystitis) (Study Days 202 to 205); (PT: AST increased) (Study Days 202 to 221); and (PT: blood creatine phosphokinase increased) (Study Days 202 to 221). The Study Investigator and the Applicant deemed the reported laboratory elevations as being unrelated to oteseconazole administration and no additional actions were taken with oteseconazole.

Clinical Reviewer: *CPK elevations and (not unexpectedly) transaminase elevations were transient and occurred 118 days (approximately 4 months) post-treatment and hence did not require study drug discontinuation. There were no reported TEAEs related to rhabdomyolysis such as myopathy or muscle pain or weakness. However, the PT: "AST increased" occurred concurrent with the CPK elevations since release of AST is associated with muscle breakdown. The subject also experienced the TEAE PT: cystitis which was treated with the Japanese third generation cephalosporin cefcapene whose side effect profile does not include CPK (but does on rare occasions affect hematologic parameters [e.g., agranulocytosis, thrombocytopenia, hemolytic anemia] and is associated with fulminant hepatitis and hepatic function disorder). The Applicant stated that they have a "high level of confidence" that the CPK elevations were not associated with oteseconazole. No causally related alternate explanations were offered.*

Possibly related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, the reviewer cannot exclude the possibility that the observed CPK elevations are related to oteseconazole exposure.*

Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole.

Subject (b) (6)

Grade 3 CPK Elevations ≥ 10 - <20 x ULN, Study Day 199 (6.6 Months) Post-OTE Exposure

A 43-year-old White, non-Latino female with no relevant prior medical history outside of the condition under study, RVVC, had a baseline (Study Day 1) CPK value wnl at 66 U/L. Subject received 87 days of treatment. Nearest post treatment CPK values, on Study Day 115 (29 days post-treatment) demonstrated Grade 1 CPK elevations of 445 U/L (2.3 x ULN). On Study Day 285, 199 days (6.6 months) following the final oteseconazole dose, the participant was reported to experience, a **Grade 4 CPK** elevation of 2649 U/L (13.8 x ULN). Subsequent CPK values obtained on Study Days 280 and 323 were 100 U/L and 140 U/L, respectively, and returned to normal limits. On the same day (Study Day 285) this CPK elevation was observed, the participant was found to have a **Grade 3 AST** elevation (99 U/L, 3.2 x ULN) and a **Grade 1 ALT** elevation (46 U/L, 1.4 x ULN). Subsequent AST and ALT laboratory values, on Study Days 289 and 323, also returned to normal. No significant pre-, peri- or post- event K⁺, phosphate, and Ca²⁺, laboratory abnormalities were noted following the observed CPK elevation. The subject had a single concomitant medication begun pre-treatment and continued throughout the study, an oral drospirenone/ethinyl estradiol contraceptive pill (Yasmin). The subject had no reported TEAEs.

***Clinical Reviewer's Assessment:** The identified CPK elevations were transient and occurred 199 days (6.6 months) after the final dose of oteseconazole. An earlier Grade 1 CPK elevation 2.3 x ULN was observed 30 days post treatment. Neither the observed CPK elevation nor the transaminase elevations were reported as TEAEs. Upon inquiry, the Applicant reported that they had a "high level of confidence" that the observed CPK findings were unrelated to the study treatment. No alternate explanations for the observed findings were offered.*

***Unlikely related:** The event occurred nearly 7 months after oteseconazole exposure and although the CPK elevations occurred within 5 half-lives, given the timing of the elevations, it is less likely that this observation was related to oteseconazole exposure.*

Subject (b) (6)

Grade 3 CPK Elevations (10 - <20 x ULN), Study Day 206 (4.1 Months Post-OTE Exposure)

A 36-year-old White, non-Latino female with no relevant prior medical history outside of the condition under study, RVVC, and no reported concomitant medications either before, during or after oteseconazole administration, had a baseline (Study Day 1) CPK of 85 U/L (wnl). A CPK value of 67 U/L (wnl) was obtained around the time of oteseconazole completion (Study Day 91). On Study Day 206, 123 days after the final dose of oteseconazole (4.1 months afterwards), the subject was observed to have a **Grade 3 CPK** elevation of 2,396 U/L (12.5 x ULN) with simultaneous mild **Grade 1 AST** elevation of 48 U/L (1.5 x ULN) not much outside of the bounds from the baseline (Study Day 1) value of 13 U/L. Related laboratory values such as ALT, Cr, K⁺, phosphate, and Ca²⁺, exhibited no prior, peri- or post event laboratory abnormalities and remained within normal limits. A single reported TEAE was coded to (PT: blood creatine

phosphokinase increased) (Study Day 206 to 211). The Applicant reported that they have “a high level of confidence” that the witnessed CPK elevations were unassociated with receipt of oteseconazole.

Clinical Reviewer: *As with the other CPK elevations described in other study subjects, Subject 21148-103 also had a transient, self-limited CPK elevation >10x ULN, that returned to baseline levels with no required intervention(s) on the part of the Study Investigator who, like the Applicant, did not believe the finding to be related to oteseconazole administration since it occurred 123 days (4.1 months) after the final oteseconazole dose. As in other cases, CPK elevations occurred simultaneously with AST elevations but no elevations in ALT, Cr or other electrolyte parameters in which abnormalities may co-occur in the settings of CPK elevations. The Applicant offered no alternative explanations for the reported CPK elevations.*

17.4.2. CPK Elevations-CL-012

Subject (b) (6)

Grade 3 CPK Elevation 10 - <20 x ULN) Study Day 127, 36 Days Post-Oteseconazole Exposure

A 29-year-old Black/African-American, non-Latino female with no pertinent past medical history (e.g., ongoing herpes simplex virus infection, acne, abdominoplasty) had baseline Study Day 1 CPK values of 94 U/L (wnl). The subject received the final dose of oteseconazole on Study Day 92. A CPK value taken on Study Day 85 was within normal limits at 93 U/L. On Study Day 127, 36 days after final receipt of oteseconazole, the was reported to have had a **Grade 3 CPK** elevation of 3044 (15.9 x ULN). Repeat laboratories obtained 3 weeks later, on Study 145, were within normal limits at 101 U/L, as were all subsequent CPK values collected on Study Days 162 187, 250 and 351. Mild, concurrent Grade 2 AST elevations occurred on Study Day 127 but soon returned to normal limits on Study Day 145, with a value of 20 U/L. All subsequent AST values remained within normal limits. Unlike AST, ALT laboratory results collected on Study Day 127 were wnl at 26 U/L and remained wnl for the entirety of the study. Cr and relevant electrolytes, K⁺, phosphate, and Ca²⁺, remained wnl pre-, during, and post-event. Pre-treatment concomitant medications were Valtrex, ethinyl estradiol acetate (Junel), spironolactone, and tinidazole and were not believed to be related to the observed CPK elevations. While the observed CPK elevation was not reported as a TEAE, the subject was reported to have three TEAEs (e.g., bacterial vaginosis, respiratory tract congestion, and cough) all of which were unrelated to the observed event and had no temporal relationship to the event.

Clinical Reviewer: *Subject (b) (6) experienced a transient, self-limited Grade 3 CPK (15.9 x ULN) elevation 43 days after administration of final oteseconazole dose. The Study Investigator did not report this event as a TEAE and deemed the event unrelated to oteseconazole treatment by the Applicant. As in other instances the observed CPK elevations were associated with mild (Grade 1) AST elevations. The Applicant provided no alternative explanation to account for the rise in CPK values.*

Possibly related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug’s long half-life, the reviewer cannot exclude the possibility that the observed CPK elevations are related to oteseconazole exposure.*

Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole.

Subject (b) (6)

Grade 2 [6- < 10 x ULN], Study Day 88; and Grade 3 CPK Elevations 10- < 20 x ULN) [8.0 Months Post-OTE Treatment]

A 40-year-old White, non-Latino female with no relevant prior medical history outside of the studied condition, RVVC, had a baseline (Study Day 1) CPK value of 50 U/L. Subject completed oteseconazole prophylaxis on Study Day 84. A Study Day 88, Grade 2 CPK laboratory value of 1820 (9.5 x ULN) was obtained. A repeat laboratory test on Study Day 95 demonstrated a return to normal CPK values. CPK values remained wnl until Study Day 320 (237 [7.9 months] days post-oteseconazole prophylaxis) when a **Grade 3 CPK** elevation of 2582 (13.5 x ULN) was observed. No subsequent CPK values were reported. On both Study Days 88 and 320, the subject experienced Grade 1 AST elevations of 58 U/L and 51 U/L, respectively. Likewise, the subject experienced Grade 1 ALT elevations 57 U/L and 51 U/L, respectively, on these days. Cr and relevant electrolytes, K⁺, phosphate, and Ca²⁺, remained wnl pre-, during, and post-event. There were no reported TEAEs.

Clinical Reviewer's Assessment: Subject (b) (6) experienced two transient, self-limited Grade 3 (9.5 x ULN) and Grade 4 (13.5 x ULN) CPK elevations on Study Day 88 (4) days post-oteseconazole administration and Study Day 320, respectively, with concomitant mild Grade 1 AST and ALT elevations. None of these CPK elevations were reported as TEAEs, nor were there any other reported TEAEs. All other Cr and related electrolytes remained within normal limits. The Applicant determined that due to the lack of a temporal nature between the CPK elevations and oteseconazole administration that the elevations were unrelated to the study drug.

Unlikely related: The event occurred 8 months after oteseconazole exposure and although the CPK elevations occurred within 5 half-lives, given the timing of the elevations, it is less likely that this observation was related to oteseconazole exposure.

Subject CL-012 (b) (6)

Grade 3 CPK Elevations, 10- < 20 x ULN, Study Day 17

A 21-year-old White, non-Latino Ukrainian female with no pertinent prior medical history outside of RVVC. The only concomitant medication pre-, during, and post therapy was the oral contraceptive tablet esogestrel. Subject had no reported TEAEs during study. Study Day 1 CPK value was 61 U/L. However, on Study Day 17, the subject was observed to have a **Grade 3 CPK** of 2630 U/L (13.7 x ULN) which soon declined to a normal CPK value of 123 U/L on Study Day 24. All subsequent CPK values, collected on Study Days 46 and 130, remained within normal limits. Subject withdrew consent from study participation on Study Day 213. Subject experienced a concomitant **Grade 2 AST** elevation of 84 U/L (2.7 x ULN) also on Study Day 17, with subsequent AST values soon afterwards returning to normal. Subject was also observed to have a **Grade 1 ALT** elevation of 58 (1.8 x ULN) on Study Day 17 which returned to normal on subsequent laboratory recordings. Cr and relevant electrolytes (K⁺, phosphate, and Ca²⁺) remained wnl pre-, during, and post-event. Subject was observed to have elevated K levels of 5.2

mEq/L and 5.3 mEq/L on Study Days 1 and 17. Subject had no evidence of hypophosphatemia at any time during the study but was observed to have a very mild and likely unrelated phosphate elevation post-event (4.7 mg/dL).

Clinical Reviewer: Subject (b) (6) experienced a single transient, self-limited Grade 3 (13.7 x ULN) CPK elevation on Study Day 17 while actively in receipt of oteseconazole, along with simultaneous Grade 2 and 1 AST and ALT elevations, respectively co-occurring that same day. The Applicant reported having a “high level of confidence” that the observed CPK elevation had no association to oteseconazole exposure. There was no other associated or relevant TEAEs, including elevations in Cr or other electrolyte values. Subject was able to complete the oteseconazole maintenance phase through the expected Study Day 87. The subject withdrew study consent on Study 213 from start of oteseconazole administration.

Probably related: Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug’s long half-life, with the event occurring within the timeframe of the drug’s first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.

17.4.3. CPK Elevations-CL-017

Subject CL-017 (b) (6)

Grade 4 CPK Elevation (≥ 20 x ULN), Study Day 103 (19 Days Post-OTE Exposure)

A 36-year-old White, Latino female whose medical history and concomitant medications were previously described above, had a Study Day 1 CPK value of 134. Subject notably had a prior history of hyperthyroidism and Graves’ disease diagnosed prior to study entry. Study Day 1 CPK value of 134 U/L was within normal limits. Subject received the final dose of oteseconazole on Study Day 85. Approximately 3 weeks post oteseconazole exposure, subject was noted to have the first of several CPK elevations, with the first elevation beginning on Study Day 103 (19 days post-treatment) with an observed **Grade 4 CPK** elevation of 8082 U/L (42.1 x ULN). CPK level then declined to 210 U/L (Grade 1) a week later on Study Day 110. However, 103 days post-oteseconazole treatment (3.4 months), on Study Day 187 the participant had a **Grade 3 CPK** elevation of 3165 (16.5 x ULN) (103 days post oteseconazole administration). Three days later, on Study Day 191 (107 days post oteseconazole administration), the subject developed a Grade 4 CPK elevation of 14833 U/L (77.3 x ULN). A subsequent CPK value declined to Grade 1 level and then finally to normal levels on the final 3 Study Days 306, 333, and 390 (CPK values of 81-96).

The subject was observed to develop a **Grade 3 ALT** of 187 U/L (6.0 x ULN) on Study Day 103. These declined on subsequent laboratory tests, only to increase on Study Day 191 to a Grade 3 elevation of 284 U/L (9.2 x ULN). All subsequent AST values returned to normal. On Study Day 103, the subject’s ALT increased to a Grade 1 ALT level of 49 U/L (1.5 x ULN) from a normal baseline level. There was a second rise in ALT values of 100 U/L on Study Day 191. All repeat CPK values from Study Days 236 through 390 remained within normal range. Cr and

relevant electrolytes, (K^+ , phosphate, and Ca^{2+}), remained largely wnl pre-, during, and post-event. The subject had a total of nine reported TEAEs with the most pertinent laboratory abnormalities being: blood creatine phosphokinase increased during Study Days 103-110 and Study Days 187-208) and concomitant (PT: myalgia Study Day 187-219).

Clinical Reviewer's Assessment: Subject (b) (6) experienced three post-oteseconazole treatment TEAEs captured in two TEAEs coded to the PT: "Blood creatine phosphokinase levels increased" all occurring 19, 103, and 107 days post-oteseconazole exposure and peaking to Grade 3 and Grade 4 elevations from normal baseline levels. Outside of a single dose of fluconazole administered on Study Day 114-115, all other concomitant medications were vitamins (magnesium, multivitamins and Vitamin C) which had begun prior to study onset. The Applicant posits that the observed CPK findings are unrelated to oteseconazole therapy because they occurred in post-treatment. No alternative explanations were offered.

Subject CL-017 (b) (6)

Grade 4 CPK Elevation ($\geq 20 \times$ ULN), Study Day 343 (8.6 Months Post-OTE Exposure)

A 21-year-old White, Latino female with no relevant medical history whose sole concomitant medication was ethinyl estradiol; norgestimate (Sprintec) oral birth control pill. Subject had no additional reported TEAEs during the study period. Subject had a Study Day 1 CPK value of 71 U/L, within normal limits. Subject received the final dose of oteseconazole on Study Day 85. All post-treatment CPK laboratories were wnl. On Study Day 343, 259 days (8.6 months) after final oteseconazole exposure, subject was witnessed to have a **Grade 4** CPK elevation of 7516 ($38.8 \times$ ULN). No subsequent CPK values were collected or reported following Study Day 343. On Study Day 343, there were simultaneous Grade 3 and Grade 2 AST (173 U/L, $5.6 \times$ ULN) and ALT (91 U/L, $2.8 \times$ ULN) elevations, respectively. Cr and relevant electrolytes (K^+ , phosphate, and Ca^{2+}), remained largely wnl pre-, during, and post-event.

Clinical Reviewer's Assessment: Subject (b) (6) experienced a Grade 4 CPK elevation on Study Day 343, 259 days following oteseconazole exposure. This finding was accompanied by AST and ALT elevations. Other potentially related lab parameters (Cr, K^+ , Phos, and Ca^{2+}) were unaffected. The Applicant did not consider the timing of these CPK elevations, 259 days post-treatment to be attributable to the study drug due to the lack of a temporal relationship and stated they had "a high level of confidence" this was not associated with oteseconazole.

Unlikely related: The event occurred nearly 9 months after oteseconazole exposure and although the CPK elevations occurred within 5 half-lives, given the timing of the elevations, it is less likely that this observation was related to oteseconazole exposure.

Subject (b) (6)

Grade 3 CPK Elevation (10 to $< 20 \times$ ULN); Study Days 255 and 258 (5.8 Months Post-OTE Exposure)

A 49-year-old White, non-Latino female with a relevant prior medical history most noted for hypothyroidism and menopause for which pre-treatment concomitant medications included levothyroxine 50 micrograms and liothyroxine 5 micrograms daily, and estradiol, progesterone, and testosterone. Subject had a baseline CPK of 76 U/L. Subject completed final dose of dose of

oteseconazole on Study Day 83. Five days post-oteseconazole therapy, on Study Day 87, subject developed a **Grade 1 CPK** elevation of 277 U/L (1.4 x ULN). A repeat CPK on Study Day 97 showed that the subject's CPK had returned to a normal level of 108. Subsequent CPK values collected on Study Days 129 thru 226 remained wnl.

However, on Study Days 255, 173 days (5.8 months post-treatment) after final oteseconazole administration, subject developed a **Grade 3 CPK** elevation of 2724 U/L (14.2 x ULN), which was followed by a decline on Study Day 258 (176 days after final oteseconazole dose) only to rise again to a **Grade 3 CPK** value of 1998 U/L (Grade 3, 10.4 x U/L). The Applicant reported no additional CPK elevations after Study Day 258. Coinciding with the reported Grade 3 CPK elevations were a Grade 1 AST elevation of 49 U/L (1.6 x ULN) and a Grade 2 AST elevation of 83 U/L (2.7 x ULN) on Study Days 255 and 258, respectively. The subject was only observed to have a single out of bound ALT value, a Grade 1 ALT elevation of 39 U/L (1.2 x ULN). All other ALT values, including those collected on Study Days 87 and 255 were wnl. All other relevant laboratory parameters, (Cr, K⁺, phosphate, and Ca²⁺) were not impacted by the Study Day 255 and 258 CPK elevations. The subject's only AEs were coded to the PT: headache (Study Days 1, Study Days 13 -109), for which subject received the concomitant ibuprofen as needed on these same days.

Clinical Reviewer: Subject (b) (6) experienced a minor Grade 1 CPK elevation on Study Day 87, followed by two additional Grade 3 CPK elevations 173 and 176 days after post oteseconazole therapy on Study Days 255 and 258, respectively. Mild AST elevations were observed in parallel with these Grade 3 CPK elevations. All other relevant lab parameters (Cr, K⁺, Phos, and Ca²⁺) were unremarkable. Subject had no temporally associated AEs (PTs: headache x 2) or concomitant medications (ibuprofen as needed) that are potentially attributable to the observed CPK elevations. The Applicant concluded that the observed lab abnormalities were unlikely to be related to oteseconazole given the lack of a temporal relationship between oteseconazole administration and the timing of the lab elevations. No alternative explanations for the observed CPK elevations were reported by the Applicant.

Unlikely related: The event occurred nearly 6 months after oteseconazole exposure and although the CPK elevations occurred within 5 half-lives, given the timing of the elevations, it is less likely that this observation was related to oteseconazole exposure.

17.4.4. CPK Elevations-CL-006

Subject (b) (6) (OTE 150 mg x3 Months)

Grade 4 CPK Elevation (≥20 x ULN) Study Day 262 (3.2 Months Post-OTE Exposure)

A 23-year-old White, non-Latino female with no relevant prior medical history (e.g., acne, allergy induced asthma, seasonal allergies, etc.). Relevant concomitant medications were Paraguard intravaginal contraceptive, topical nystatin (Study Day 71 to73) and vaginal Terazol 3 (Study Day 78-80). Reported TEAEs were coded to PT: seborrheic dermatitis (Study Day 8) and PT: vulvovaginal discomfort (Study Day 69 to 73). Subject received their final dose of oteseconazole on Study Day 168. Their baseline (Study Day 1) was within normal limits at 89. Subsequent CPK levels remained wnl for the duration of study treatment up through Study Day 157 when subject was observed to have a **Grade 1 CPK** elevation of 231 U/L (1.1 x ULN). The

subject completed the final day of oteseconazole on Day 168. Repeat laboratory testing demonstrated a **Grade 4 CPK** elevation of 6541 U/L (31 x ULN) on Study Day 262 (95 days, 3.2 months post-oteseconazole). However, subsequent CPK values obtained 12 days later, on Study Day 273 and then on Study Day 332 showed that CPK values had returned to normal levels. The subject experienced a simultaneous mild **Grade 2 AST** elevation of 75 U/L (2.2 x ULN) on Study Day 262. Repeat AST values remained wnl. ALT values were negligibly elevated on Study Day 157 (37 U/L) and otherwise were unimpacted by the observed Study Day 262 CPK elevations, as were other relevant laboratory results (Cr, K⁺, phosphate, and Ca²⁺) that demonstrated minimal to no abnormal elevations.

***Clinical Reviewer:** Subject (b) (6) had a Grade 1 CPK elevation on Study Day 157 while still on treatment (which was completed on Study Day 168). The Applicant attributed this elevation to oteseconazole. Approximately 3 months after oteseconazole exposure the subject experienced Grade 4 CPK elevations that were associated with minor Grade 2 AST elevations, with no significant elevations in ALT values or other pertinent lab parameters. There were no relevant temporally related TEAEs or concomitant medications that could explain the observed CPK elevations.*

***Possibly related:** The subject experienced a very mild, asymptomatic elevation in CPK relatively early in the treatment course that did not require any adjustments to oteseconazole therapy with values shortly returning to normal. Subject experienced a second, more impressive, unexplained elevation in CPK within 3 months post-oteseconazole exposure for which the Applicant could provide no alternative explanation.*

Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, the reviewer cannot exclude the possibility that the observed CPK elevations are related to oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole.

Subject (b) (6) (OTE 150 mg x3 Months)

Grade 3 CPK Elevation (10 to <20 x ULN), Study Day 35

A 22-year-old White, non-Latino female with no relevant medical history or concomitant medications outside of a pre-treatment oral contraceptive pill. Subject received final dose of oteseconazole on Study Day 169. Subject had a reported Study Day 1 CPK value of 67 U/L (wnl). On Study Day 35, the subject was observed to have a **Grade 3** on treatment **CPK elevation of 3164 U/L (15.3 x ULN)**. CPK returned to normal levels on Study Day 59 (73 U/L) only rise again to a Grade 1 elevation of 251 U/L on Study Day 91. All subsequent CPK testing yielded results that remained wnl. Study Day 35 CPK elevations coincided with a transient mild **Grade 1 AST** elevation of 79 U/L (2.3 x ULN); however, on subsequent testing all AST had returned to normal levels. Likewise, a transient, mild Grade 1 ALT elevation of 46 U/L was also observed on Study Day 46 U/L (1.4 x ULN), with all subsequent values within normal limits. Other relevant laboratory results (Cr, K⁺, phosphate, and Ca²⁺) remained unaffected by the observed Study Day 91 CPK elevations. Reported TEAEs of PT: smear cervix abnormal, skin lesion, and abdominal pain, lower were unrelated to the observed both in timing and relatedness to the event. CPK elevations, were notably not captured as TEAEs despite occurring on Study

Day 35. In their assessment of the Grade 3 CPK elevations, the Applicant deemed that the elevations may be attributable to oteseconazole administration.

***Clinical Reviewer:** Subject (b) (6) experienced a transient, Grade 3 CPK elevation on Study Day 35, with simultaneous, transient Grade 1 AST and ALT elevations. All of which returned to normal limits in all subsequent observations. The Applicant deemed that the CPK elevations may be attributable to oteseconazole dosing.*

***Probably related:** The subject experienced asymptomatic CPK elevations relatively early in the treatment course that did not require any adjustments to oteseconazole therapy and returned to normal. Subject experienced a second, mild on treatment episode of CPK elevations, which was also asymptomatic and less elevated than the first episode. No alternate explanations were offered by the Applicant.*

Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, with the event occurring within the timeframe of the drug's first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.

Subject (b) (6) (OTE 150 mg x3 Months)

Grade 2 CPK elevation (6-<10 x ULN), Study Day 244 (2.3 months post-OTE treatment)

A 22-year-old Black/African-American, non-Latino female with no relevant medical history outside of a prior history of bacterial vaginosis and chlamydial infections. Initial documented CPK of 131 U/L (wnl) was collected on Study Day 12 (there was no Study Day 1 CPK result). Subject received their final dose of oteseconazole on Study Day 175.

Noted concomitant medications included:

- Flagyl x 2 doses for recurrent BV infections (Study Days 34 - 41; Study Days 109-116);
- Fluconazole for RVVC (Study Days 161 - 164); and
- Bactrim DS for UTI (Study Days 180 - 188).

Subject experienced TEAEs coded under PT:

- BV infections x 3 (Study Days 34 to 41; Study Day 97 – 116; Study Day 247 - 280);
- Vulvovaginal burning sensation (Study Days 55 -90; Study Days 103-132); and vulvovaginal discomfort (Study Days 55- 90; Study Days 103 - 132)
- UTI (Study Days 172-188).

CPK values remained wnl thru Study Day 244, 70 days (2.3 months) after the final oteseconazole dosing, when subject experienced a **Grade 2 CPK** elevation of 1629 U/L (7.7 x ULN). Repeat testing approximately 2 weeks later demonstrated CPK values had returned to normal. CPK elevations were accompanied by a very mild, transient **Grade 1 AST** elevation of 45 U/L (1.3 x ULN) on Study Day 244 which returned to normal levels on subsequent testing. There were no observed simultaneous Study Day 244 ALT elevations. Other relevant laboratory

results (Cr, K⁺, phosphate, and Ca²⁺) remained unaffected by the observed Study Day 244 CPK elevation.

Clinical Reviewer: Subject (b) (6) experienced a transient, Grade 2 CPK elevation on Study Day 244 (70 days post-oteseconazole treatment), with simultaneous, transient Grade 1 AST and ALT elevations. All of which returned to normal limits in all subsequent observations. Neither TEAEs nor listed concomitant medications appear to be attributable to the observed CPK elevation. The Applicant determined that the observed elevation was “unlikely related to oteseconazole exposure due to its temporal relationship (2 months post final dose) and its transient nature.

Probably related: Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug’s long half-life, with the event occurring within the timeframe of the drug’s first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.

Subject (b) (6) (OTE 300 mg x3 Months)

Grade 4 CPK elevation ($\geq 20 \times$ ULN) (Study Day 57)

A 27-year-old White, non-Latino female with no relevant medical history outside of a prior history of asthma, attention deficit disorder, and the condition under study. Concomitant medications both pre-enrollment and throughout the study included the oral contraceptive pill (Lo Loestrin) and Adderall. Final day of oteseconazole exposure was on Study Day 168.

Subject (b) (6) had a Study Day 1 CPK value of 77 U/L wnl. On Study Day 57, the subject experienced a transient **Grade 4 CPK** elevation of 4869 U/L (23.1 x ULN), with repeat testing on Study Day 83 (approximately one month afterwards) showing a return to normal CPK levels. CPK remained wnl during the rest of the subject’s participation in the study. The subject had a **Grade 1 AST** elevation of 77 U/L (2.3 x ULN) and a very minor concomitant ALT elevation of 34 U/L (1.03 x ULN) on Study Day 57. Both AST and ALT levels returned to normal on subsequent testing on Study Day 83 and for the rest of the subject’s participation in the study. Other relevant laboratory tests (Cr, K⁺, phosphate, and Ca²⁺) remained unaffected by the observed Study Day 57 CPK elevation.

Clinical Reviewer: Subject (b) (6) experienced a transient, Grade 4 CPK elevation on Study Day 57, while undergoing active oteseconazole treatment. CPK elevations were accompanied by transient, minor Grade 1 AST elevation and a negligible ALT elevation. Other relevant labs (Cr, K⁺, Phos, and Ca²⁺) were unimpacted by this rise in CPK. This increased CPK was not identified by the Study Investigator as a TEAE despite the event occurring while the subject was on active treatment and the $>20 \times$ ULN rise. It is unlikely that concomitant medications were the cause of the observed elevation as they were longstanding pre-treatment medications. Reported TEAEs were unrelated to the observed CPK elevation and there were no accompanying TEAEs of myalgia, muscle pain or weakness. The Applicant reported that they did not believe this event

to be related to the study drug due to the transience of the observed laboratory elevations. No alternate explanations were provided by the Applicant.

Probably related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, with the event occurring within the timeframe of the drug's first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.*

Subject (b) (6) (OTE 300 mg x6 Months)

Grade 4 CPK elevation of 38,141 U/L (180.8 x ULN), Study Day 58 (on active treatment)

A 26-year-old White, Latino female with no relevant medical history outside of a prior history of chlamydia infection (b) (6) BV infection (b) (6) a previous history of depression (b) (6) (b) (6) and anxiety (b) (6) and the condition under study. Concomitant medications both pre-enrollment and during the study period included Mirena birth control (b) (6) topical Mycolog (nystatin and triamcinolone acetonide cream) for *candida* infection (Study Days 171 -196); Macrobid for a UTI (Study Days 179 -185), and pre-enrollment oral vitamin B12. Subject had a single, unrelated TEAE PT: urinary tract infection (Study Days 171-185). Subject (b) (6) received final dose of oteseconazole on Study Day 168.

Subject (b) (6) had a baseline (Study Day 1) CPK value of 123 U/L. CPK remained wnl until Study Day 58 when the subject was witnessed to have a Grade 4 CPK elevation of 38,141 U/L (180.8 x ULN). A week later, on Study Day 64, CPK values were observed to decline to Grade 1 elevation of 1049 U/L (5.0 x ULN). From Study Day 78 and onward until the end of the subject's study participation their CPKs remained wnl. These Study Day 58 and Study Day 64 CPK elevations were accompanied by concomitant Grade 4 AST (515 U/L; 15 x ULN) and Grade 1 AST elevations (66 U/L; 1.9 x ULN). Similar to the observed CPK elevations, the subject's subsequent AST values remained wnl starting from Study Day 78 onwards. The subject simultaneously experienced short-lived Grade 2 ALT elevations of 108 U/L (3.3 x ULN) and Grade 1 ALT elevation of 71 U/L (2.2 x ULN) on Study Days 58 and 64, respectively. Other relevant laboratory results (Cr, K⁺, phosphate, and Ca²⁺) remained unaffected by the observed Study Day 58 CPK elevations.

Clinical Reviewer: *Subject (b) (6) experienced a transient, on treatment Grade 4 CPK elevation of 38,141 U/L on Study Day 58 which declined to a Grade 1 elevation one week afterwards on Study Day 64. This all occurred while the subject was actively receiving oteseconazole treatment. The Applicant reasoned that the observed Grade 4 CPK elevation and the associated Grade 4 and 2 AST and ALT elevations, respectively, were unrelated to oteseconazole administration "since the elevated CK values were transient they were unlikely related to OTE dosing." The observed CPK and transaminase levels were not identified as TEAEs by either the Study Investigator or the Applicant. There were no reported rhabdomyolysis related symptoms, such as myalgia, muscle weakness, associated with this observed elevation. Nor could the subject's prior medical history or concomitant medications (e.g., nystatin/triamcinolone cream*

and nitrofurantoin capsules [associated with hepatitis but not CPK elevations]) adequately explain the observed findings either in the timing of the occurrence or in the side effect profile.

Probably related: *Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug's long half-life, with the event occurring within the timeframe of the drug's first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.*

Subject (b) (6) (OTE 300 mg x3 Months)

Grade 4 CPK elevation ($\geq 20 \times$ ULN), Study 256 (3.0 months post-OTE exposure)

A 27-year-old Asian, non-Latino female with no relevant prior medical history outside of notable conditions as ongoing migraines ((b) (6) – ongoing), dysmenorrhea ((b) (6) – ongoing); and heartburn ((b) (6)-ongoing). Notable concomitant medications included pre-enrollment medications: tums for heartburn (2006-ongoing); aspirin for migraines ((b) (6) – ongoing); herbal tea/health supplement ((b) (6)-ongoing); amino acid energy supplement ((b) (6) - ongoing) and Dayquil and Nyquil cold & flu on Study Days 201 -204 for PT upper respiratory tract infection (Study Days 201-206)—none of which appeared to be associated with the observed CPK elevations.

Reported TEAEs had no apparent relevance temporal or otherwise to the witnessed CPK elevations and included the PTs:

- Upper respiratory tract infection (Study Days 13-8; Study Days 201-206; Study Days 311-336)
- Arthralgia (Study Day 14 - 46). Subject (b) (6) received the final dose of oteseconazole (from the start of oteseconazole) on Study Day 168, with a corresponding CPK of 67 U/L (Study Day 166)

Subject displayed a normal baseline (Study Day 1) CPK of 110 U/L. On Study Day 7, subject was observed to have a near negligible CPK elevation of 214 U/L (1.0 x ULN) with subsequent CPK values remaining wnl through Study Day 158 when the subject sustained a **Grade 1** elevation of 457 (2.2 x ULN). On Study Day 249 (82 days [2.7 months] post-oteseconazole exposure) the participant experienced a Grade 2 CPK elevation of 1678 U/L (8.0 x ULN). Retesting one week, on Study Day 256 showed an even higher Grade 4 CPK elevation of 4557 U/L (21.6x ULN) (89 days post-oteseconazole, 3.0 months). Repeat testing approximately two weeks later, on Study Day 271 demonstrated that from that timepoint onwards CPK values had returned to normal limits. AST values corresponding with the Study Day 249 and 256 CPK elevations also demonstrated moderate **Grade 2 AST** 86 U/L (2.5 x ULN) and severe **Grade 3 AST** 179 U/L (5.3 x ULN) elevations, respectively, that returned to normal levels from Study Day 271 through the end of participation. ALT also had corresponding, yet transient Grade 0 (36 U/L, 1.1 x ULN) and Grade 2 (86 U/L, 2.6 x ULN) elevations on Study Day 249 and Study Day 256, respectively, all of which returned to normal on Study Day 271 through the end of the subject's study participation on Study Day 340. Other relevant laboratory results (Cr, phosphate, and Ca²⁺) remained unaffected by the observed Study Day 249 and 256 CPK elevations. The

subject was noted to have elevated K+, but still Grade 0, potassium value from the time of screening through the end of the study and were not believed to be related to that study drug.

Clinical Reviewer: Subject (b) (6) experienced a Grade 4 CPK elevation of 4,557 U/LL on Study Day 256, 3.0 months post-oteseconazole exposure. As in nearly all other cases, the witnessed CPK elevation was accompanied by equally transient but often mild to moderate concomitant AST and ALT elevations. Neither the CPK nor the transaminase elevations were identified by either the Study Investigator or the Applicant as TEAEs even with Grade 3 and 4 elevations. The Applicant suggested that “Since the higher elevated CK values were recorded three months after the final 300-mg OTE dose, and subsequently returned to normal, the temporal relationship suggests the elevated CK value is unrelated to OTE.” They ascribed the elevations to the subject URIs. While nasopharyngitis/upper respiratory infections were relatively common in the Phase 2b and 3 trials, most other CPK elevations did not occur in the setting of URIs and vice versa. Other relevant labs (Cr, K⁺, Phos, and Ca²⁺) remained unaffected by the observed Study Day 249 and 256 CPK elevations.

Probably related: Given the totality of CPK elevations observed throughout the oteseconazole Phase 1-3 development program coupled with the drug’s long half-life, with the event occurring within the timeframe of the drug’s first half-life (although the subject was no longer actively receiving the study day), the reviewer cannot exclude the possibility that the event is associated with oteseconazole exposure. Increased CPK elevations have also been reported to occur in azoles—itraconazole and voriconazole. A causal mechanism of action between the drug and the event has yet to be elucidated.

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17.5. Phase 2/3 Pregnancy Summary Listings

Table 185. Pregnancy Listing - Phase 2/3 RVVC Pool

Subject ID	Study	OTE or Placebo	Estimated Due Date	Birth Outcome (If Applicable)	Timing (weeks)	Congenital Anomaly	Breastfeeding
(b) (6)	CL-011	Placebo	(b) (6)	Healthy, live birth			
	CL-011	OTE		Healthy, live birth	Pre-pregnancy (-14 ⁻⁴ to -2 ⁻⁶ weeks) Pre-14 days to 2 weeks pre -pregnancy	Unknown	Unknown
	CL-011	OTE		Healthy, live birth; C-section	Pre-pregnancy and 1 st trimester	None	Yes (<3 weeks)
	CL-011	Placebo		Not reported			
	CL-012	OTE		Not reported	1 st trimester		
	CL-012	Placebo		Healthy, live birth			
	CL-012	OTE		Healthy, live birth	Pre-pregnancy (-31 ⁻⁶ to -20 ⁺⁰ weeks)	None	Yes (11 months and ongoing)
	CL-012	OTE		Healthy, live birth; C-section	Pre-pregnancy (-19 ⁻¹ to -7 ⁻² weeks)	None	Yes (10 months and ongoing)
	CL-012	Placebo		Healthy, live birth; C-section			
	CL-012	Placebo		Elective termination			
	CL-012	OTE		Not reported	Pre-pregnancy (-23 ⁺³ to 16 ⁺¹ weeks)		
	CL-012	OTE		Healthy, live birth	Pre-pregnancy (-44 ⁺³ to -32 ⁺³ weeks)	None	Yes (6 months and ongoing)
	CL-012	OTE		Not reported	Pre-pregnancy (-44 ⁺⁶ to -30 ⁺⁶ weeks)		
	CL-017	OTE		Elective termination	Pre-pregnancy (-16 ⁺⁴ to -4 ⁺⁴ days)		
	CL-017	OTE		Elective termination	Pre-pregnancy (-38 ⁺³ to -26 ⁺³ weeks)		
	CL-017	OTE		Spontaneous abortion	Pre-pregnancy (-10 ⁺¹ to 1 ⁺⁶ weeks)		
	CL-017	OTE		Healthy, live birth; C-section	Pre-pregnancy (-29 ⁺⁴ to -17 ⁺⁴ weeks)	None	No
	CL-017	Placebo		Healthy, live birth; C-section			

Subject ID	Study	OTE or Placebo	Estimated Due Date	Birth Outcome (If Applicable)	Timing (weeks)	Congenital Anomaly (b) (6)	Breastfeeding
(b) (6)	CL-017	OTE	(b) (6)	Healthy, live birth	Pre-pregnancy (-32 ⁻² to -20 ⁺² weeks)	None	Yes (6 months and ongoing)
	CL-006	OTE		Elective termination	Pre-pregnancy and 1 st trimester		
	CL-006	OTE		Elective termination	Pre-pregnancy and 1 st trimester		
	CL-006	OTE		Healthy, live birth	2 nd and 3 rd trimester	Unknown	Unknown
	CL-006	OTE		Elective termination	Pre-pregnancy (-41 ⁻¹ to -17 ⁻² weeks)		
	CL-006	OTE		Healthy, live birth	Pre-pregnancy (-24 ⁻⁵ weeks to -6 days)	Unknown/Healthy and no CA as of (b) (6) (5 months of age)	Unknown
	CL-006	OTE		Healthy, live birth	Pre-pregnancy and 1 st trimester	Unknown	Unknown
	CL-006	OTE		Spontaneous abortion	Pre-pregnancy (-38 ⁻³ to -14 ⁻⁴ weeks)		
	CL-006	OTE		Healthy, live birth	Pre-pregnancy and 1 st trimester	None	Yes (2 weeks)
	CL-006	OTE	Unknown [‡]	Elective termination	Pre-pregnancy and 1 st trimester		
	CL-006	OTE	Unknown ^{**}	Chemical pregnancy	Pre-pregnancy and 1 st trimester		
	CL-006	Placebo		Chemical pregnancy			
	CL-006	Placebo		Healthy, live birth			
	CL-006	Placebo		Healthy, live birth			

Source: Patient Safety Database

Modified from Applicant's Table 39. Pregnancy Listing-Phase 2/3 RVVC Pool, page 159 from Applicant's submission titled "Summary of Clinical Safety." The added EDC was based on the Applicant's submitted study report. Timing was calculated based on the EDC.

[†]Calculated based on ultrasound at 5 weeks. Her LMP on the narrative is (b) (6) appears to be in error.

^{††}Although her EDC was unknown, her positive UPT was on (b) (6)

*EDC populated from Applicant submitted case narrative by the reviewer.

[‡] EDC was not determined, date of positive UPT was (b) (6). Serum HCG was not done. Ultrasound was not reported. The subject terminated the pregnancy (b) (6) by taking mifepristone. Her LMP was (b) (6).

**EDC not determined, patient presented with positive urine and serum beta HCG tests on (b) (6) and then 12 days later it became negative. Subject received test drug on (b) (6) to (b) (6)

Abbreviations: IP, investigational product; OTE, oteseconazole; RVVC, recurrent vulvovaginal candidiasis a. Date of positive pregnancy test or start of last menstrual period.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Mechanism of Action

Oteseconazole (OTE), VT-1161, is an azole metalloenzyme inhibitor targeting the fungal sterol, 14 α demethylase (CYP51), which mediates membrane permeability and fluidity by demethylating the 14 α position of lanosterol thereby affecting an early step in the biosynthesis of ergosterol. In a study comparing the binding affinity of clotrimazole, fluconazole, voriconazole, itraconazole and OTE to *C. albicans* CYP51 it was found that OTE has a greater affinity for the peptides that form the backbone of CYP51, than itraconazole and voriconazole (Hoekstra et al. 2014; Warrilow et al. 2014). Oteseconazole was shown to be unique with now detectable to the human cytochrome, HsCYP51, at the concentrations studied.

Resistance

Azole resistance in *Candida albicans* may be due to various resistant mechanisms such as efflux pump over expression, over expression of *CYP51*, mutations in *ERG11* or an alteration in ergosterol biosynthesis. To identify determinants of oteseconazole resistance, the influence of specific azole resistance mechanisms on oteseconazole, when placed in a fluconazole-susceptible strain, SC5314, was evaluated (Nishimoto et al. 2019). Increased *CDR1* and *CDR2* expression through the activation of the transcriptional activator of *CDR1* activation of the (*TAC1*) gene, a zinc cluster transcription factor (*ZCFs*) that regulates *CDR1* and *CDR2*, increased oteseconazole MICs >8 fold compared to the susceptible parent strain suggesting that the overexpression of the *TAC1* transcription factor and *CDR1* is associated with increased oteseconazole MICs. Similar effects were observed with voriconazole which increased MICs 16-fold compared to the parent strain. Therefore, it appears that drug efflux via *CDR1* expression is associated with an increase in oteseconazole MIC.

In another experiment, the effect of a gain of function mutation in multidrug resistance regulator 1 (*Mrr1*), a *ZCF* that controls the expression of *MDR1*, a major facilitator transporter, that prevents drug accumulation in yeast cells, was examined. Mutations in *Mrr1* was associated with a 4-fold increase in oteseconazole MIC, suggesting that *MDR1* transporter is possibly involved in resistance. An increase in MIC values was also observed with fluconazole and voriconazole. In another experiment, the effects of different alterations in the azole target enzyme on *C. albicans* susceptibility to oteseconazole was investigated. Amino acid substitutions in the Egr11 (another *ZCF*) resulted in a 4-16-fold increases in oteseconazole MIC values.

Animal Studies

The efficacy of VT-1161 was evaluated in a number of animal models infected with *C. albicans* and *C. glabrata* but are not directly related to VVC or RVVC.

1. In a Murine Estrogen-Dependent model, mice were administration estradiol and then infected with *C. albicans* ATCC 3153A into the vagina. Three days after infection, the mice were treated orally with 4, 10, and 25 mg/kg, of oteseconazole and 25 mg/kg fluconazole for 4 days and the fungal burden was measured in vaginal lavage solutions 1- and 4- days post-treatment. Each

oteseconazole dose, at both time points, was significantly superior to vehicle-treated control animals in suppressing vaginal fungal burden (p value <0.0002). In comparing the 2 agents, oteseconazole and fluconazole, at the same time points, there was no significant difference. Both suppressed fungal burden by >99% compared with control, and both cleared the same percent of animals (~70%) of detectable fungus.

2. In a neutropenic mouse candidiasis model, female CD-1 mice were inoculated by tail vein with 0.1 mL of 2.7×10^5 CFU/mL *C. albicans* R303 strain. VT-1161, terbinafine or no treatment (control) were administered at 2 hours after infection by oral gavage. The concentrations of VT-1161 were 5, 10 and 20 mg/kg and colony forming units (CFU) of homogenized kidneys were determined. A dose response was observed with VT-1161 with mean $\log_{10}$ CFU/kidney ranging from 2.74 to 4.39 at 24 hours post-infection, compared to 5.10 $\log_{10}$ CFU/kidney for the nontreated control. Mice treated with terbinafine had a fungal burden in the kidneys comparable to the nontreated control.

3. The efficacy of VT-1161 was compared to amphotericin B, caspofungin and fluconazole in a mouse model of *Candida* kidney infection. A concentration of 0.1 mL of 1.22×10^5 CFU/mL was used to establish infection. Mice (10 per group) infected with *C. albicans* were administered VT-1161 (2, 5, 10 or 20 mg/kg) or fluconazole (2, 5, 10 or 20 mg/kg) orally once per day on days 1 through 4. All kidneys were collected at death or the end of study and the fungal burden was determined. Survival was measured up to 18 days post-infection. The median survival time in untreated animals was 5 days. VT-1161 exhibited a dose dependent survival benefit, mice treated with 10 mg/kg or higher had 100% survival. The median survival time for animals treated with 2 mg/kg VT-1161 was extended to 14 days. In comparison, mice treated with 2, 5, 10 and 20 mg/kg fluconazole had median survival times of 6.5, 11, 12.5 and >18 days. All mice treated with 1 mg/kg amphotericin B or 0.25 mg/kg caspofungin survived.

4. The efficacy of VT-1161 against *C. glabrata* was evaluated in a female CD-1 neutropenic, mouse candidiasis systemic infection model. The mice were infected with 0.1 mL of 7.5×10^6 CFU/mL *C. glabrata* strain R363. Treatment (5 or 20 mg/kg) was administered by tail vein injection 2 hours after inoculation according to body weight. Kidneys and blood were collected from four mice in each group on day 5 and all surviving mice in the VT-1161 treatment groups on day 19. Survival was assessed on Day 19. Nearly all mice survived when treated with any dose (5 or 20 mg/kg) of VT-1161; however, survival was dose dependent in mice treated with fluconazole. The MIC for VT-1161 against this strain was 0.06 mcg/mL against *C. glabrata* (n=10) wild type clinical isolates and 2 mcg/mL against 10 isolates characterized as azole resistant.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

The OSI clinical inspection summary reported some discrepancies in investigators' total composite VVC signs and symptoms scores and mycology culture test results and reliability concerns related to accidental unblinding events and subject ineligibility. The data generated by these sites were otherwise acceptable. These issues are discussed in Section 10, Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure.

21. Labeling Summary of Considerations and Key Additional Information

Prescribing Information

General

This Prescribing Information (PI) review includes a high-level summary of the major changes made to the PI submitted by the Applicant on May 27, 2021.

HIGHLIGHTS OF PRESCRIBING INFORMATION

The Established Pharmacologic Class (EPC was changed from (b) (4) to “azole antifungal” based on the [FDA EPC Text Phrases for Indications and Usage heading in Highlights \(updated October 2021\)](#) and [Determining the EPC for Use in Highlights guidance. Refer to Section 21 for additional details.](#)

The remainder of the **HIGHLIGHTS** and the **TABLE OF CONTENTS** sections of the PI were revised for consistency with the rest of the Prescribing Information.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Vulvovaginal Candidiasis

The proposed indication (b) (4) was changed because the information provided by the Applicant was insufficient to support this indication. Based on the data submitted, VIVJOA (oteseconazole) is indicated to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC, who are not of reproductive potential. Refer to Section 1.2.2 of this document for additional details.

The change in the terminology (b) (4) to “reduce the incidence of RVVC” is supported (b) (4)

2. DOSAGE AND ADMINISTRATION

(b) (4)

An alternate fluconazole/VIVJOA dosage regimen was added because this was (b) (4) Section [II.6.1](#) of this review for additional details.

(b) (4)

(b) (4) Retained instructions for administration of VIVJOA with food since this is how VIVJOA was studied in the clinical trials and there is uncertainty about efficacy under fasted conditions. Refer to Section [II.8.2.1](#) of this review for additional details.

4. CONTRAINDICATIONS

- Contraindications in females of reproductive potential and pregnant and lactating women were added based on the ocular abnormalities observed in animal studies and the prolonged drug exposure window of approximately 690 days (based on 5 times the half-life) of oteseconazole that precludes adequate risk mitigation of potential risks associated with VIVJOA use. Refer to Section [II.7.6](#) of this review for additional details.
- A contraindication in patients with hypersensitivity was added based on the demonstrated cases of hypersensitivity observed with the use of VIVJOA in the clinical trials. Refer to Sections [II.7.6.7](#); [III.17.3.3](#) of this review for additional details.

5. WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

A warning and precaution describing the risk of embryo-fetal toxicity was added based on animal studies that indicated VIVJOA may cause fetal harm. A statement regarding the drug exposure window of approximately 690 days (based on 5 times the half-life of oteseconazole) precluding adequate mitigation of the embryo-fetal toxicity risks was added to the Warnings and Precautions and subsections 8.1 and 8.3 of the PI. Refer to Section [I.2.2](#) and [II.7.6](#) of this review for additional details.

6. ADVERSE REACTIONS

Presentation of safety information including most frequently reported adverse reactions, and other less common adverse reactions from the three VIVJOA clinical trials was modified to highlight safety from the three trials separately due to the differences in the comparator groups, as opposed to the Applicant's proposal to display pooled safety adverse reactions from all three trials. Refer to Section [II.7.6](#) of this review for additional details.

A commentary on the elevations in creatinine phosphokinase (CPK) that were observed in the patients treated with VIVJOA compared to the comparator groups was added. Refer to Sections [II.7.6.6](#), [II.7.7.2](#), and [III.17.4](#) of this review for additional details.

A disclaimer statement was added to avoid implied use of VIVJOA in females of reproductive potential as follows: “Although females of reproductive potential were included in the clinical safety data, VIVJOA is contraindicated in females of reproductive potential because of a risk of embryo-fetal toxicity [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1, 8.3)*].”

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy, 8.2 Lactation and 8.3 Females of Reproductive Potential

Based on the benefit/risk analysis for oteseconazole, including the concerning ocular abnormalities observed in the animal studies, the inability to exclude the risk of cataracts in humans and the prolonged drug exposure window of approximately 690 days (based on 5 times the half-life) of oteseconazole, the contraindication statement for use in females of reproductive potential and pregnant women lactating women was added. Additional details on the ocular abnormalities observed in animal studies and the Agency’s current definition of females who are not of reproductive potential were included in this section of the PI. Refer to Sections [I.2.2](#) and [II.8.4](#) of this review for additional details.

8.4 Pediatric Use

A contraindication statement in females of reproductive potential was added. (b) (4)

(b) (4)
(b) (4) VIVJOA is not recommended for use in pre-menarchal pediatric patients. Refer to Section [II.8.3](#) of this review for additional details.

8.6 Renal Impairment

A statement on the use of VIVJOA in patients with renal impairment was added to indicate that no dosage adjustment is recommended in patients with mild to moderate renal impairment. However, VIVJOA is not recommended for use in patients with severe renal impairment or end-stage renal disease (ESRD) with or without dialysis. These labeling recommendations were based on pharmacokinetic analysis. Refer to Section [II.8.1](#) of this review for additional details.

8.7 Hepatic Impairment

A statement on the use of VIVJOA in patients with hepatic impairment was added to indicate that clinically relevant differences in the safety of VIVJOA between patients with mild hepatic impairment (Child -Pugh A) and the indicated population were not expected. However, VIVJOA is not recommended for use in patients with moderate to severe hepatic impairment due to insufficient information. These labeling recommendations were based on pharmacokinetic analysis. Refer to Section [II.8.1](#) of this review for additional details.

12. CLINICAL PHARMACOLOGY

12.4 Microbiology

The list of microorganisms associated with RVVC was modified based on the in vitro susceptibility data that was submitted to the NDA. Refer to Section [II.3.1](#) of this review for additional details.

13. NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Data regarding the increased incidences of hemorrhage were added to highlight the possible effects of long-term exposure to high doses of oteseconazole. This information was added to this subsection because it was considered to be significant animal data necessary for the safe and effective use of VIVJOA in humans that is not incorporated in other sections of the PI as delineated in 21 CFR 201.57(14)(ii). Refer to Section [1.2.2](#) of this review for additional details.

14 CLINICAL STUDIES

The clinical studies discussed in Section 14 of the PI included effectiveness and safety data for females of reproductive potential. A disclaimer statement was added to note that VIVJOA is contraindicated in females of reproductive potential to avoid implying the use of the VIVJOA in this population as delineated in 21 CFR 201.57(c)(15)(i) that emphasizes that any clinical study discussed in Section 14 must not imply or suggest indications or uses not stated in the Indications and Usage section of the PI. The addition of the disclaimer statement was based on the recommendations noted in section II.B of the guidance for industry: [Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format](#) (January 2006) that indicates that if such studies are included in Section 14 of the PI, “the limitations of the study and the reasons for inclusion should be stated.” The disclaimer statement added to Section 14 was as follows: Although females of reproductive potential were included in the clinical efficacy data, VIVJOA is contraindicated in females of reproductive potential because of a risk of embryo-fetal toxicity [see *Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)*].

The use of rescue VVC medication is an intercurrent event that confounds the assessment of a possible culture-verified recurrence at a later timepoint. Furthermore, the use of additional VVC medication was noted to be higher on the oteseconazole arm compared to placebo in subjects for who a culture verified episode was not reported. Ignoring the use of rescue medication overestimates the effect of treatment with oteseconazole. Therefore, the results of the sensitivity analysis that treats VVC medication use as an event were added for each trial. Refer to Section [6.3.1](#) for additional details.

(b) (4)

For Trial 017, it was expected that subjects who failed to resolve their infection at Day 14 would be considered events in the primary analysis. The results presented were revised based on this definition. Refer to Section [6.2.3.3](#) for additional details.

(b) (4)

(b) (4)

Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Patient Information
- Carton labeling
- Container label

22. Postmarketing Requirements and Commitments

The following Postmarketing Commitments were agreed to by the Applicant:

4221-1: Conduct in Vitro Drug Interaction Studies Evaluating Oteseconazole as a Substrate or Inhibitor of MATEs (MATE1 and MATE2-K).

Final Report Submission date: July 2022.

The goal of this in vitro study is to evaluate the potential for MATE-transporter mediated drug-drug interactions with oteseconazole by determining whether oteseconazole is a substrate or inhibitor of this transporter. Data from this study will determine the need for dedicated clinical drug-drug studies with oteseconazole and MATE transporter substrates and inhibitors.

4221-2: Complete the Five Ecotoxicity Studies That Are Currently in Progress and Submit the Results of the Assays.

Final Report Submission date: May 2022.

Five ecotoxicity study reports listed in Table 2 of the Mycovia response to the October 7, 2021, Information Request (IR) are needed to support the categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb.

23. Financial Disclosure

Table 186. Covered Clinical Studies: CL-011 and CL-012

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 162		
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)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Studies: CL-017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 51		
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)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Studies: CL-006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 33		
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)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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NDA 215888
Vivjoa (oteseconazole)

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25. Review Team

Table 187. Reviewers of Integrated Assessment

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Nonclinical Team Leader	Terry Miller, PhD
Clinical Microbiology Reviewer	Lynette Berkeley, PhD, MT (ASCP)
Clinical Microbiology Team Leader	Avery Goodwin, PhD
OCP Reviewers	Henrietta Abodakpi, PharmD, PhD Meng Wang, PhD
OCP Team Leaders	Dakshina Chilukuri, PhD
OCP/Pharmacometrics Reviewer	Elyes Dahmane, PhD
OCP/Pharmacometrics Team Leader	Justin Earp, PhD
Clinical Reviewer	Caroline J. Jjingo MD, MPH
Clinical Team Leader	Thomas Smith, MD
Statistical Reviewers	Kyungyul Lee, PhD (Primary Reviewer) Cheryl Dixon, PhD (Secondary Reviewer)
Supervisory Statistician	Karen M. Higgins, ScD
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Division Director (pharm/tox)	Hanan Ghantous, PhD
Deputy Division Director (OCP)	Zhixia (Grace) Yan Danielsen, PhD
Division Director, Regulatory Project Management	Maureen Dillon-Parker, MS, RAC
Associate Director of Labeling	Abimbola Adebowale, PhD
Deputy Division Director	Dmitri Iarikov, MD, PhD
Division Director (clinical)	Peter Kim, MD, MS
Office Director (or designated signatory authority)	Adam Sherwat, MD

OCP=Office of Clinical Pharmacology
OB=Office of Biostatistics

Table 188. Additional Reviewers of Application

DPMH Reviewer	Wenjie Sun, MD
DPMH Team Lead	Miriam Dinatale, DO
DPMH Deputy Director for Safety (Acting)	Leyla Sahin, MD
DPMH Division Director	Lynne Yao, MD
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OMP/DMPP Reviewer	Nyedra Booker, PharmD, MPH
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OMP/OPDP Team Lead	James Dvorsky, PharmD
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OPQ/Drug Product	Hailin (Sheena) Wang, PhD (Primary Assessment) David Claffey, PhD (Secondary Assessment)
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OPQ/Environmental Analysis	James Laurenson, MS
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OSE/DEPI Reviewer	Hannah Day, PhD
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NDA 215888
 Vivjoa (oteseconazole)

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IRT for Cardiac Safety Statistical Lead	Dalong Huang, PhD
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IRT for Cardiac Safety Team Leader	Christine Garnett, PhD

IRT=Interdisciplinary Review Team
 OMP=Office of Medical Policy
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE=Office of Surveillance and Epidemiology
 OTS=Office of Translational Sciences
 DEPI=Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DO= Division of Ophthalmology
 DPMH= Division of Pediatric and Maternal Health
 DRISK=Division of Risk Management

Table 189. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Microbiology Reviewer	Lynette Berkeley, PhD, MT (ASCP)	OID/DAI	5.1 ☒ Authored ☐ Approved
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Clinical Pharmacology Reviewer	Meng Wang, PhD	OCP/DIDP	8.2,14.1-14.2 ☒ Authored ☐ Approved
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	Signature: Henrietta D. Abodakpi -S (Affiliate)		Digitally signed by Henrietta D. Abodakpi -S (Affiliate) DN: c=US, o=U.S. Government, ou=HH5, ou=FDA, ou=People, 0.9.2342.19200300.1001.1=2002018693, cn=Henrietta D. Abodakpi -S (Affiliate) Date: 2022.04.25 17:29:52 -04'00'
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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology/Pharmacometrics Reviewer	Elyes Dahmane, PhD	OCP/DPM	6.1, 7.7.2, 8.1, 14.3 ☒ Authored ☐ Approved
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Pharmacology/Toxicology	Terry Miller, PhD	OND/DPT-ID	13 ☐ Authored ☒ Approved
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Pharmacology/Toxicology	Hanan Ghantous, PhD	OND/DPT-ID	13 ☐ Authored ☒ Approved
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Product Quality	Dorota Matecka, PhD	OPQ/DNDP I	9 ☒ Authored ☒ Approved
Tertiary Reviewer	Signature: Dorota M. Matecka -S Digitally signed by Dorota M. Matecka -S Date: 2022.04.25 15:11:32 -04'00'		
Clinical	Caroline Jjingo, MD, MPH	OID/DAI	2, 3, 7.3-7.7,8.3- 8.4,10,11,16.5,17, 23 ☒ Authored ☐ Approved
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Chief, Regulatory Project Management Staff	Signature: Gregory Dibernardo -S Digitally signed by Gregory Dibernardo -S Date: 2022.04.25 14:15:33 -04'00'		
Regulatory Project Management	Maureen Dillon- Parker, MS, RAC	ORO/DRO-ID/Enter division	12 ☐ Authored ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
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Cross-Disciplinary	Abimbola Adebawale, PhD	OID/DAI	21 ☒ Authored ☒ Approved
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Clinical	Peter Kim, MD, MS	OID/DAI	Enter sections. ☐ Authored ☒ Approved
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Deputy Director	Signature: Adam I. Sherwat -S		Digitally signed by Adam I. Sherwat -S Date: 2022.04.25 20:50:56 -04'00'

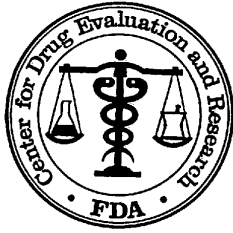
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

GREGORY F DIBERNARDO
04/26/2022 10:12:47 AM

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04/26/2022 10:24:00 AM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	IND 111675
Drug Name:	VT-1161
Indication(s):	(b) (4) (b) (4) recurrent vulvovaginal candidiasis (RVVC) (b) (4)
Studies	One Two Year Oral Gavage Carcinogenicity Study in Rats and One Six-Month Oral Gavage Carcinogenicity Study in rash2 Transgenic Mice.
Applicant:	Sponsor: Mycovia Pharmaceuticals Inc 4505 Emperor Boulevard, Suite 300 Durham, NC 27703 USA Test facility: (b) (4)
Documents Reviewed:	Electronic submission: November 19, 2020 via SN0086
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Pharmacology/Toxicology for Infectious Diseases
Reviewing Pharmacologist:	Owen G. McMaster, PhD
Project Manager:	Gregory F. Dibernardo
Keywords:	Carcinogenicity, Dose response

Table of Contents

- 1. Background..... 3

- 2. Rat Study 3
 - 2.1. Sponsor's analyses..... 4
 - 2.1.1. Survival analysis..... 4
 - Sponsor's findings 4
 - 2.1.2. Tumor data analysis..... 4
 - Adjustment for the multiplicity: 5
 - Sponsor's findings 5
 - 2.2. Reviewer's analyses 5
 - 2.2.1. Survival analysis..... 5
 - Reviewer's findings: 6
 - 2.2.2. Tumor data analysis..... 6
 - Multiple testing adjustments: 7
 - Reviewer's findings: 7

- 3. Mouse Study 8
 - 3.1. Sponsor's analyses..... 9
 - 3.1.1. Survival analysis..... 9
 - Sponsor's findings 9
 - 3.1.2. Tumor data analysis..... 9
 - Sponsor's findings 10
 - 3.2. Reviewer's analyses 10
 - 3.2.1. Survival analysis..... 10
 - Reviewer's findings 10
 - 3.2.2. Tumor data analysis..... 10
 - Multiple testing adjustment: 11
 - Reviewer's findings: 11

- 4. Summary..... 11
 - Rat Study: 11
 - Mouse Study: 12

- 5. Appendix 14

- 6. References: 32

1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of VT-1161 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice. Results of this review have been discussed with the reviewing pharmacologist Dr. McMaster.

In this review, the phrase "dose response relationship" (trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, and one vehicle control group. Two hundred and eighty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals, as indicated in Table 1. The dose levels for the three treated groups were 0.5, 1.5, 5 mg/kg/day for males and females, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle [0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water], administered orally by gavage for about 104 weeks in the same manner as the treated groups. Both male and female rats in the 5 mg/kg/day (high) dose group had similar clinical findings and body weight trends; therefore, the dose level was decreased from 5mg/kg/day to 3 mg/kg/day during Week 55 for males and week 33 for females. Starting Day 478 (Week 69), the high dose males were placed on a 6-week dosing holiday, dosing resumed on Day 520 (Week 75) and that group (high) was terminated early during Week 77 due to survival reaching 20 animals in the group. All other male groups were terminated during Week 90 due to survival in the vehicle control group reaching 20 animals. Also, in female rats, due to early termination criteria, the study was terminated early based on high mortality/low survivability, animal in group 1, 3, and 4 were terminated during Week 86, groups 2 were terminated during Week 84.

The change of dosing was not taken into consideration by the sponsor for determination of a weighted dose to be used for the group in the statistical analysis.

Table 1: Experimental Design in Rat Study

Group Name	Group N0.	Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
Vehicle Control	1	0	0	70	70
Low	2	0.5	0.5	70	70
Medium	3	1.5	1.5	70	70
High	4	5/3 [#]	5/3 [#]	70	70

Males in group 1, 2, and 3 were terminated during Week 90, groups 4 were terminated during Week 77. Females in group 1, 3, and 4 were terminated during Week 86, groups 2 were terminated during Week 84.

[#]: Dose reduced from 5 mg/kg/day to 3 mg/kg/day began on Day 379 (Week 55) for males and on Day 225 (Week 33) For females.

During the administration period, all animals were checked for morbidity, mortality, injury, and the availability of food and water twice daily, once in the morning and once in the afternoon. The animals were removed from the cage, and detailed observations were conducted for each animal prior to randomization on Day -2 and for each surviving main study animal weekly during the study. On occasion,

clinical observations were recorded at unscheduled intervals. Detailed examinations for palpable masses were done weekly, the time of onset, location, size, appearance, and progression of each grossly visible or palpable mass, observed in carcinogenicity rats, was recorded weekly any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations included, but were not limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, nervous system effects including tremors, convulsions, reactivity to handling, and unusual behavior, and the palpation of masses. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights for all animals were measured and recorded at receipt, prior to randomization and once weekly for the first 14 weeks, every two weeks until Week 28, every four weeks thereafter for the duration of the study, and on the day of the scheduled terminal necropsy.

2.1. Sponsor's analyses

2.1.1. Survival analysis

The Kaplan-Meier's curves were presented graphically for male and female rats separately. An overall test for survival was used to compare the homogeneity of survival rates across the groups using a log-rank test at the 0.05 significance level. If the survival rates were significantly different ($p < 0.05$), then a follow up analysis was done where each treatment group was compared to vehicle control group using a log-rank test.

Any animal with accidental injury that causes its death, or its unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of rats surviving to their terminal necropsy were 20 (28.6%), 19 (27.1%), 16 (22.8%), and 20 (28.6%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (27.1%), 20 (28.6%), 32 (45.7%), and 25 (35.7%) in the vehicle control, low, medium, and high dose groups, in female rats, respectively. The sponsor's report concluded that, there was a statistically significant difference in mortality between the high dose groups and the vehicle control group in male rats $p < 0.01$.

2.1.2. Tumor data analysis

Tumor incidence data were analyzed within each sex, using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test was calculated, and Fisher's exact test was used to compare each treatment group with the control groups. The Cochran-Armitage trend test was applied for all control and treatment groups and was arranged in a strictly increasing dose level. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al. The cut-off points for the interval-based test were Weeks 0 to 52, 53 to 78, 79 to before terminal sacrifice, and the terminal sacrifice. Actual dose levels were used as the scores. All tumors in the scheduled terminal sacrifice interval were considered incidental for the purpose of statistical analysis.

The Poly-3 method was also used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights were displayed. The tests of significance included both an overall trend and pair-wise comparisons of each treatment group with the corresponding control. All p-values are reported using upper-tailed tests.

Adjustment for the multiplicity:

For multiplicity testing adjustment, the sponsor used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons. Site-specific background historical control database was used to determine whether the tumors should be designated as rare or common.

Sponsor's findings:

Following the multiple testing adjustment method described above, the sponsor's analysis showed, statistically significant VT-1161-related neoplastic findings occurred in the thyroid gland, liver, testes, and uterus.

Neoplastic findings in the thyroid gland consisted of benign follicular cell adenoma in both sexes at ≥ 1.5 mg/kg/day and malignant follicular cell carcinoma in the thyroid gland in males at ≥ 1.5 mg/kg/day and females at 5/3 mg/kg/day. The neoplastic findings in the liver consisted of an increased incidence, of benign hepatocellular adenomas in males at ≥ 0.5 mg/kg/day and malignant hepatocellular carcinomas in females at 5/3 mg/kg/day. The neoplastic findings in the testes consisted of a statistically significant increased incidence of benign Leydig (interstitial) cell adenomas at ≥ 1.5 mg/kg/day. And the neoplastic findings in the uterus consisted of an increased incidence of benign granular cell tumors at 5/3 mg/kg/day.

2.2 Reviewer's analyses

To verify sponsor's analysis and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed the survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically on December 13, 2018 via SN0001.

It was noticed that, the dose level was decreased from 5mg/kg/day to 3 mg/kg/day during Week 55 for males and week 33 for females. Starting Day 478 (Week 69), the high dose males were placed on a 6-week dosing holiday, dosing resumed on Day 520 (Week 75) and that group (high) was terminated early during Week 77 due to survival reaching 20 animals in the group. All other male groups were terminated during Week 90 due to survival in the vehicle control group reaching 20 animals. Also, in female rats, due to early termination criteria, the study was terminated early based on high mortality/low survivability, animal in group 1, 3, and 4 were terminated during Week 86, groups 2 were terminated during Week 84.

The change of dosing for each sex/treatment group was taken into consideration in the determination of a weighted dose to be used in the statistical analysis, the weighted dose levels would be 4.2 and 3.8 for high dose groups in male and female rats, respectively.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curves were presented graphically for male and female rats separately. The

dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for male and female rats, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20 (28.6%), 19 (27.1%), 16 (22.8%), and 20 (28.6%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (27.1%), 20 (28.6%), 32 (45.7%), and 25 (35.7%) in the vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed a statistically significant increase in mortality across the vehicle control group and the three treated groups in male rats ($p < 0.0001$). The pairwise comparisons showed statistically significant increase in mortality between the high dose groups and the vehicle control group in male rats ($p = 0.0016$). However, in female rats, the pairwise comparisons showed a statistically significant decrease in mortality between the medium dose group and the vehicle control group ($p = 0.0185$).

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method, an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of $s_h = 1$. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of

$s_h = \left(\frac{w_h}{w_{\max}} \right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score

$s_h = 1$ can be considered as a whole animal, while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104-week standard rat and mouse studies, a value of $k=3$ is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used $k=3$ for the analysis of the data. Based on the intent to treat (ITT) principle $W_{\max}$ was considered as 104 for both male and female rats.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 5, 15, and 42 for male rats and 0, 5, 15, and 38 for female rats) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male rats and female rats, respectively.

Multiple testing adjustments:

Following the FDA more recently revised draft guidance for the carcinogenicity study design and data analysis 2015, for the two-year rat study this reviewer used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

A tumor is defined as a rare tumor if the published spontaneous rate or the spontaneous rate of the vehicle control of the tumor is less than 1%, and a common tumor is defined as one with tumor rate greater than or equal to 1%.

Reviewer's findings:

Table 2: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons Treated Groups and Vehicle Control Group in Rats

Sex	Organ Name	Tumor Name	0 mg Vehicle Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Male	Liver	Adenoma, Hepatocellular, Benign	0/70 (29) 0.1263	4/70 (33) 0.0734	8/70 (35) 0.0053*	2/70 (16) 0.1212
		Adenoma, Hepatocellular, Benign/Malignant	1/70 (29) 0.0804	4/70 (33) 0.2201	8/70 (35) 0.0273 [®]	3/70 (16) 0.1212
	Testes	Adenoma, Leydig Cell, Benign	1/70 (29) <0.0001*	5/70 (33) 0.1300	12/70 (38) 0.0033*	15/70 (25) <0.0001*
	Thyroid Gland	Adenoma, Follicular Cell, Benign	2/70 (29) <0.0001*	6/70 (34) 0.1860	36/70 (50) <0.0001*	27/70 (33) <0.0001*
		Carcinoma, Follicular Cell, Malignant	1/70 (29) 0.0162 [®]	2/70 (32) 0.5375	13/70 (37) 0.0014*	4/70 (17) 0.0549
		Adenoma, Follicular Cell, Benign/ Malignant	3/70 (30) <0.0001*	8/70 (35) 0.1477	44/70 (53) <0.0001*	29/70 (34) <0.0001*
Female	Liver	Carcinoma, Hepatocellular, Malignant	0/70 (26) 0.0169*	0/70 (28) NC	0/70 (30) NC	3/70 (30) 0.1465
	Thyroid Gland	Adenoma, Follicular Cell, Benign	0/70 (26) <0.0001*	2/70 (29) 0.2734	12/70 (37) 0.0007*	28/70 (43) <0.0001*
		Carcinoma, Follicular Cell, Malignant	0/70 (26) 0.0010*	0/70 (28) NC	2/70 (32) 0.3001	6/70 (32) 0.0224*
		Adenoma, Follicular Cell, Benign/Malignant	0/131 (52) <0.0001*	2/129 (56) 0.2665	13/127 (65) 0.0003*	32/129 (57) <0.0001*
	Uterus with Cervix	Granular Cell Tumor, Benign	2/70 (28) 0.0018*	1/70 (29) 0.8880	6/70 (34) 0.2003	10/70 (34) 0.0269 [®]

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed. NC = Not calculable.

*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.

[®]: Not statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively

Following the multiple testing adjustment method described above, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated

groups for the incidence of benign adenoma leydig cell in Testes, of benign adenoma, follicular Cell, and of the combined benign adenoma, follicular Cell and malignant carcinoma follicular Cell, in thyroid gland of male rats (p-value <0.0001, <0.0001, and <0.0001, respectively). The pairwise comparisons test showed statistically significant increase in tumor incidences of benign adenoma leydig cell in Testes, of benign adenoma, follicular cell, and of the combined benign adenoma, follicular cell and malignant carcinoma follicular cell, in thyroid gland in medium and high dose group, when compare to the vehicle control group in male rats (p-value=0.0033, <0.0001, <0.0001, and <0.0001, <0.0001, <0.0001, respectively). Also, the pairwise comparisons test showed statistically significant increase in tumor incidences of benign adenoma, Hepatocellular in liver, and malignant carcinoma follicular Cell, in thyroid gland in the medium dose group, when compare to the vehicle control group in male rats (p-value=0.0053, and =0.0014, respectively).

In female rats, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups for the incidence of malignant carcinoma, hepatocellular in the liver, of benign adenoma, follicular Cell, malignant carcinoma follicular cell and of the combined benign adenoma, follicular Cell and malignant carcinoma follicular cell, in thyroid gland, and, of benign granular cell tumor, in the uterus with cervix (p =0.0169, <0.0001, =0.0010, <0.0001, and <0.0018, respectively). The pairwise comparisons showed statistically significant increases in the medium and high doses group for the incidences of benign adenoma, follicular Cell, and of the combined benign adenoma, follicular cell and malignant carcinoma follicular cell, in thyroid gland, when compared to the vehicle control group in female rats (p = 0.0007, 0.0003 and <0.0001, <0.0001, respectively). Also, the pairwise comparisons showed a statistically significant increase in the high dose group for the incidence of malignant carcinoma follicular cell in the thyroid gland, when compared to the vehicle control group (p=0.0224), as indicated in Table 2.

Reviewer's comment on a minor discrepancy between the SEND data set and the .xpt data set of the male rat experiment

Animal 4059 in the high dose group of male rats was recorded as dying accidentally "ACCIDENTAL DEATH", at week 78 in n the DS domain of the SEND data, which means DTHSACST = 4 (Accidental death) based on the format of the tumor.xpt. However, in the XTP data, it was recorded as a natural death, and was labelled as "DTHSACST = 1". However, this minor discrepancy between the two datasets did not affect the results of reviewer's survival and tumor data analyses.

3. Mouse Study

Two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and fifteen rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 15 animals. The dose levels for the three treated groups were 0.5, 1.5, and 5 mg/kg/day for males and 1.5, 5, and 15 mg/kg/day for females, for up to 26 weeks, as indicated in Table 1. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with one intraperitoneal dose of 75 mg/kg NMU, N-methyl-N-nitrosourea on Day 1 of the dosing phase. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water.], were administered in the same manner as the treated groups.

Table 1: Experimental Design in Mouse Study

Group Name	Group N0.	Target Dose Level (mg/kg/day)		Number of Animal	
		Male	Female	Males	Females
		Vehicle Control	1	0	0
Low	2	0.5	1.5	25	25
Medium	3	1.5	5	25	25
High	4	5	15	25	25
Positive Control	5	75	75	15	15

Animals in group 6 were dosed with one intraperitoneal dose of positive control article on Day 1 of the dosing phase.

Group 1 received vehicle control article only

During the administration period, all animals were checked for morbidity, mortality, injury, and availability of food and water, twice daily (a.m. and p.m.), abnormal findings were recorded for toxicity animals as they were observed. Cage side observations were conducted for each carcinogenicity animal at least twice daily, except on days when detailed observations were conducted. Abnormal findings or an indication of normal was recorded, any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively was euthanized. Observations will include, but will not be limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, nervous system effects including tremors, convulsions, reactivity to handling, unusual behavior, and palpation of tissue masses. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights were recorded Within three days of arrival, at least once prior to randomization and/or Day -1, and once weekly for the first 14 weeks, every two weeks thereafter.

3.1. Sponsor's analyses

3.1.1 Survival analysis

Intercurrent mortality data will be analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups were conducted using a log-rank test. If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis will be done where each treatment group will be compared to the control group using a log-rank test. Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests.

Sponsor's findings:

Sponsor's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 24 (96%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in male mice, respectively, and 23 (92%), 24 (96%), 25 (100%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in females, respectively. The sponsor's report concluded that, there were no statistically significant differences in mortality amongst the groups for both males and females when data of the positive control group were excluded.

3.1.2 Tumor data analysis

Tumor incidence data will be analyzed using both survival adjusted and unadjusted tests. The unadjusted tests will be based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test will be calculated, and Fisher's exact test will be used to compare each treatment

group with the control group. Trend test will be applied for all control and treatment groups that can be arranged in a strictly increasing dose level. The survival adjusted test will be conducted according to the prevalence/mortality methods described by Peto et al (Peto et al, 1980).

The Poly-1 method will be used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights will be displayed. The tests of significance will include both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values will be reported using upper-tailed tests, unless otherwise indicated.

Multiple testing adjustment:

For multiplicity adjustment testing, the sponsor used significance levels of 0.005 and 0.025 for common and rare tumors, respectively in dose response relationship (trend) tests and significance levels of 0.01 and 0.05 for common and rare tumors, respectively in pairwise comparisons.

Sponsor's findings:

For both males and females, there were no statistically significant results at the 5% significance level,

3.2 Reviewer's analyses

Similar to the rat study, this reviewer independently performed the survival and tumor data analyses of the mouse study. For the analysis of the survival data and the tumor data of the mouse study, this reviewer used similar methodologies that were used for the analyses of the survival and tumor data of the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically.

3.2.1 Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for male and female mice, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the appendix for male and female mice, respectively. Results for test of dose response relationship and homogeneity of survivals among treatment groups are given in Tables 5A and 5B in the appendix for male and female mice, respectively.

Reviewer's findings:

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), 24 (96%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in male mice, respectively, and 23 (92%), 24 (96%), 25 (100%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in females, respectively. The reviewer's report showed no statistically significant dose response relationship in the mortality of both male and female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

3.2.2 Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and the pairwise comparisons of vehicle control and treated groups are given in Table 6A and 6B in the appendix for male and female mice, respectively.

Multiple testing adjustment:

For multiplicity testing adjustment in a transgenic mouse study, this reviewer used the level of significance of 0.05 for tests of positive dose responses and for pairwise increase comparisons for both common and rare tumor types.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VT-1161 dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any individual treated groups, when compare to the vehicle control group in both male and female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant lymphoma in multicentric neoplasm, benign papilloma, in skin, and of benign papilloma, in stomach, when compared to the vehicle control group in male mice (p-values =0.0431, =0.0040, and <0.0001, respectively). Also, the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of benign adenoma, in harderian glands, of benign papilloma, in skin, of benign papilloma, in stomach, and of benign polyp, endometrial stromal, in uterus with cervix, in female mice (p-values =0.0468, =0.0018, <0.0001, and = 0.0060, respectively).

4. Summary

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in regular rats and one in transgenic mice. These studies were intended to assess the carcinogenic potential of VT-1161 in rats and mice when administered orally by gavage at appropriate drug levels for about 104 weeks in rats and 26 weeks in mice.

Rat Study:

In this study two separate experiments were conducted, one in male rats and one in female rats. In each of these two experiments there were three treated groups, and one vehicle control group. Two hundred and eighty Sprague-Dawley rats of each sex were assigned to three treated groups and one vehicle control group by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 70 animals, as indicated in Table 1. The dose levels for the three treated groups were 0.5, 1.5, 5 mg/kg/day for males and females, for up to 104 weeks. In this review, these dose groups were referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle [0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water], administered orally by gavage for about 104 weeks in the same manner as the treated groups. Both male and female rats in the 5 mg/kg/day (high) dose group had similar clinical findings and body weight trends; therefore, the dose level was decreased from 5mg/kg/day to 3 mg/kg/day during Week 55 for males and week 33 for females. Starting Day 478 (Week 69), the high dose males were placed on a 6-week dosing holiday, dosing resumed on Day 520 (Week 75) and that group (high) was terminated early during Week 77 due to survival reaching 20 animals in the group. All other male groups were terminated during Week 90 due to survival in the vehicle control group reaching 20 animals. Also, in female rats, due to early termination criteria, the study was terminated early based on high mortality/low survivability, animal in group 1, 3, and 4 were terminated during Week 86, groups 2 were terminated during Week 84.

This reviewer's analysis showed the numbers of rats surviving to their terminal necropsy were 20 (28.6%),

19 (27.1%), 16 (22.8%), and 20 (28.6%) in the vehicle control group, low, medium, and high dose groups, in male rats, respectively, and 19 (27.1%), 20 (28.6%), 32 (45.7%), and 25 (35.7%) in the vehicle control, low, medium, and high dose groups, in female rats, respectively. This reviewer's analysis showed a statistically significant increase in mortality across the vehicle control group and the three treated groups in male rats ($p < 0.0001$). The pairwise comparisons showed statistically significant increase in mortality between the high dose groups and the vehicle control group in male rats ($p = 0.0016$). However, in female rats, the pairwise comparisons showed a statistically significant decrease in mortality between the medium dose group and the vehicle control group ($p = 0.0185$).

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups for the incidence of benign adenoma leydig cell in Testes, of benign adenoma, follicular Cell, and of the combined benign adenoma, follicular Cell and malignant carcinoma follicular Cell, in thyroid gland of male rats (p -value < 0.0001 , < 0.0001 , and < 0.0001 , respectively). The pairwise comparisons test showed statistically significant increase in tumor incidences of benign adenoma leydig cell in Testes, of benign adenoma, follicular cell, and of the combined benign adenoma, follicular cell and malignant carcinoma follicular cell, in thyroid gland in medium and high dose group, when compare to the vehicle control group in male rats (p -value $= 0.0033$, < 0.0001 , < 0.0001 , and < 0.0001 , < 0.0001 , < 0.0001 , respectively). Also, the pairwise comparisons test showed statistically significant increase in tumor incidences of benign adenoma, Hepatocellular in liver, and malignant carcinoma follicular Cell, in thyroid gland in the medium dose group, when compare to the vehicle control group in male rats (p -value $= 0.0053$, and $= 0.0014$, respectively).

In female rats, this reviewer's analysis showed statistically significant increasing dose response relationships across the vehicle control and the treated groups for the incidence of malignant carcinoma, hepatocellular in the liver, of benign adenoma, follicular Cell, malignant carcinoma follicular cell and of the combined benign adenoma, follicular Cell and malignant carcinoma follicular cell, in thyroid gland, and, of benign granular cell tumor, in the uterus with cervix ($p = 0.0169$, < 0.0001 , $= 0.0010$, < 0.0001 , and < 0.0018 , respectively). The pairwise comparisons showed statistically significant increases in the medium and high doses group for the incidences of benign adenoma, follicular Cell, and of the combined benign adenoma, follicular cell and malignant carcinoma follicular cell, in thyroid gland, when compared to the vehicle control group in female rats ($p = 0.0007$, 0.0003 and < 0.0001 , < 0.0001 , respectively). Also, the pairwise comparisons showed a statistically significant increase in the high dose group for the incidence of malignant carcinoma follicular cell in the thyroid gland, when compared to the vehicle control group ($p = 0.0224$), as indicated in Table 2.

No other significant dose response relationship or pairwise comparisons were noted in either sex.

Mouse Study:

In this study two separate experiments were conducted, one in male mice and one in female mice. In each of these two experiments there were three treated groups, one vehicle control group, and one positive control group. One hundred and fifteen rasH2 transgenic mice of each sex were assigned randomly to one of the five groups by a stratified randomization scheme designed to achieve similar group mean body weights in equal size of 25 animals except the positive control group which had 15 animals. The dose levels for the three treated groups were 0.5, 1.5, and 5 mg/kg/day for males and 1.5, 5, and 15 mg/kg/day for females, for up to 26 weeks, as indicated in Table 1. In this review, these dose groups would be referred to as the low, medium, and high dose group, respectively. The positive control group was administered with one intraperitoneal dose of 75 mg/kg NMU, N-methyl-N-nitrosourea on Day 1 of the dosing phase. This group was included to verify

sensitivity of the test system to detect carcinogenicity effect. The vehicle control group received daily oral vehicle control article only [0.5% (w/w) Carboxymethylcellulose (CMC: medium viscosity) in deionized water.], were administered in the same manner as the treated groups.

This reviewer's analysis showed the numbers of mice surviving to their terminal necropsy were 24 (96%), 24 (96%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in male mice, respectively, and 23 (92%), 24 (96%), 25 (100%), and 23 (92%) in the vehicle control, low, medium, and high dose groups, in females, respectively. The reviewer's report showed no statistically significant dose response relationship in the mortality of both male and female mice. The pairwise comparisons also showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group in either sex of mice.

For tumor data, following the multiple testing adjustment method described above, this reviewer's analysis showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased VT-1161 dose in both male and female mice. The pairwise comparisons test also showed no statistically significant increases in tumor incidences in any groups, when compare to the vehicle control group in both male and female mice.

The pairwise comparisons showed statistically significant increases in the positive control group for the incidences of malignant lymphoma in multicentric neoplasm, of benign papilloma, in skin, and of benign papilloma, and of benign papilloma in stomach, when compared to the vehicle control group in male mice (p-values =0.0431, =0.0040, and <0.0001, respectively). Also, the pairwise comparisons showed statistically significant increases in the positive control group for the incidences of benign adenoma, in harderian glands, benign papilloma, in skin, benign papilloma, in stomach, and of benign polyp, endometrial stromal, in uterus with cervix, in female mice (p-values =0.0468, =0.0018, <0.0001, and =0.0060, respectively).

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI

cc:

Archival IND 111675 - VT-1161

DR. Rahman Dr. Lin

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5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

Week	0 mg/kg/day Vehicle Control		15 mg/kg/day Low		50 mg/kg/day Medium		150 mg/kg/day High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	13	18.57	5	7.14	4	5.71	30	42.86
53 - 78	23	51.43	27	45.71	29	47.14	20	71.43
79 - 92	14	71.43	19	72.86	21	77.14	.	.
Ter. Sac.	20	28.57	19	27.14	16	22.86	20	28.57
Total	70	100.00	70	100.00	70	100.00	70	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 1B: Intercurrent Mortality Rate
Female Rats

Week	0 mg/kg/day Vehicle Control		15 mg/kg/day Low		50 mg/kg/day Medium		150 mg/kg/day High	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	8	11.43	1	1.43	5	7.14	4	5.71
53 - 78	28	51.43	33	48.57	23	40.00	32	51.43
79 - 92	15	72.86	16	71.43	10	54.29	9	64.29
Ter. Sac.	19	27.14	20	28.57	32	45.71	25	35.71
Total	70	100.00	70	100.00	70	100.00	70	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 2A: Intercurrent Mortality Comparison for
Male Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	<.0001*	0.7665	0.8729	0.0016*
Homogeneity (Log-Rank)	<.0001*	0.7633	0.8711	0.0013*

*: Statistically significant at 0.05

Table 2B: Intercurrent Mortality Comparison for
Female Rats

Test Statistics	P-value for Vehicle Cont. Low, Med, high	P-value for Vehicle Cont. vs Low	P-value for Vehicle Cont. vs Med	P-value for Vehicle Cont. vs High
Dose-Response (Likelihood Ratio)	0.2667	0.6415	0.0183*	0.2858
Homogeneity (Log-Rank)	0.0887	0.6346	0.0166*	0.2777

*: Statistically significant at 0.05

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

Organ Name	Tumor Name	male Rats Poly-3 test			
		0 mg Vehicle Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Adrenal Glands	Adenoma, Cortical, Benign	1/70 (29) 0.5503	4/70 (33) 0.2201	1/70 (32) 0.7781	1/70 (15) 0.5708
	Pheochromocytoma, Benign	5/70 (31) 0.7447	8/70 (34) 0.3335	5/70 (34) 0.6926	2/70 (16) 0.7709
	Pheochromocytoma, Malignant	1/70 (29) 0.8032	2/70 (32) 0.5375	1/70 (32) 0.7781	0/70 (15) 1.0000
	Pheochromocytoma Benign/Malignant	6/70 (31) 0.8373	10/70 (35) 0.2807	6/70 (34) 0.6906	2/70 (16) 0.8411
Bone, Tibia	Osteosarcoma, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
Brain	Granular Cell Tumor, Malignant	3/70 (30) 0.9913	2/70 (32) 0.8425	0/70 (32) 1.0000	0/70 (15) 1.0000
	Meningioma, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
	Mixed Glioma, Benign	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
	Mixed Glioma, Malignant	2/70 (29) 0.3177	3/70 (32) 0.5476	0/70 (32) 1.0000	2/70 (16) 0.4482
	Oligodendroglioma, Malignant	0/70 (29) 0.1481	0/70 (31) NC	0/70 (32) NC	1/70 (16) 0.3556
Cavity, Abdominal	Myxosarcoma, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
Coagulating Glands	Adenocarcinoma, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC
Ear, Right	Papilloma, Squamous Cell, Benign	0/70 (29) 0.7290	1/70 (31) 0.5167	0/70 (32) NC	0/70 (15) NC
Ears	Papilloma, Squamous Cell, Benign	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Head	Hair Follicle Tumor, Benign	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Heart	Schwannoma, Endocardial, Benign	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
	Schwannoma, Endocardial, Malignant	0/70 (29) 0.7290	1/70 (31) 0.5167	0/70 (32) NC	0/70 (15) NC
	Schwannoma, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC

male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Kidneys	Liposarcoma, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
Large Intestine, Cecum	Sarcoma, Undifferentiated, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Large Intestine, Colon	Sarcoma, Undifferentiated, Malignant	0/70 (29) 0.7290	1/70 (31) 0.5167	0/70 (32) NC	0/70 (15) NC
Lip	Carcinoma, Squamous Cell, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Liver	Adenoma, Hepatocellular, Benign	0/70 (29) 0.1263	4/70 (33) 0.0734	8/70 (35) 0.0053*	2/70 (16) 0.1212
	Carcinoma, Hepatocellular, Malignant	1/70 (29) 0.2619	0/70 (31) 1.0000	0/70 (32) 1.0000	1/70 (15) 0.5708
	Adenoma/Carcinoma, Hepatocellular, Benign/Malignant	1/70 (29) 0.0804	4/70 (33) 0.2201	8/70 (35) 0.0273	3/70 (16) 0.1212
Lung	Carcinoma, Squamous Cell, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Mammary Gland	Adenocarcinoma, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
	Fibroadenoma, Benign	1/70 (29) 0.2343	0/70 (31) 1.0000	1/70 (33) 0.7853	1/70 (15) 0.5708
Multicentric Neoplasm	Hemangioma, Benign	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
	Hemangiosarcoma, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC
	Leukemia, Granulocytic, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC
	Lymphoma, Malignant	2/70 (30) 0.4589	1/70 (32) 0.8926	1/70 (33) 0.8978	1/70 (15) 0.7139
	Sarcoma, Histiocytic, Malignant	0/70 (29) 0.5265	1/70 (32) 0.5246	1/70 (33) 0.5323	0/70 (15) NC
Oral Cavity	Papilloma, Squamous Cell, Benign	0/70 (29) 0.1402	0/70 (31) NC	0/70 (32) NC	1/70 (15) 0.3409
Pancreas	Adenoma, Acinar Cell, Benign	2/70 (29) 0.7260	0/70 (31) 1.0000	2/70 (33) 0.7413	0/70 (15) 1.0000
	Adenoma, Islet Cell, Benign	4/70 (30) 0.7005	1/70 (31) 0.9760	1/70 (32) 0.9780	1/70 (15) 0.8834
	Carcinoma, Islet Cell, Malignant	2/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000

male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Parathyroid Glands	Adenoma, Benign	4/70 (30) 0.9742	0/70 (31) 1.0000	1/70 (32) 0.9780	0/70 (15) 1.0000
Pituitary Gland	Adenoma, Pars Distalis, Benign	37/70 (48) 0.6694	35/70 (49) 0.8073	41/70 (53) 0.5801	19/70 (27) 0.8212
Skeletal Muscle	Fibrosarcoma, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
Skin	Basal Cell Tumor, Benign	0/70 (29) 0.7691	2/70 (32) 0.2710	0/70 (32) NC	0/70 (15) NC
	Carcinoma, Squamous Cell, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
	Fibrosarcoma, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC
	Hair Follicle Tumor, Benign	0/70 (29) 0.3510	0/70 (31) NC	2/70 (33) 0.2792	0/70 (15) NC
	Keratoacanthoma, Benign	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
	Papilloma, Squamous Cell, Benign	1/70 (29) 0.9284	1/70 (31) 0.7706	0/70 (32) 1.0000	0/70 (15) 1.0000
Skin, Subcutis	Adenoma, Basal Cell, Benign	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
	Carcinoma, Squamous Cell, Malignant	0/70 (29) 0.1852	1/70 (31) 0.5167	0/70 (32) NC	1/70 (15) 0.3409
	Fibroma, Benign	1/70 (29) 0.2831	1/70 (32) 0.7781	2/70 (33) 0.5491	1/70 (15) 0.5708
	Fibrosarcoma, Malignant	1/70 (29) 0.5670	5/70 (34) 0.1386	3/70 (34) 0.3692	1/70 (16) 0.5899
	Fibroma, Benign/ Fibrosarcoma, Malignant	2/70 (30) 0.4031	6/70 (35) 0.1845	5/70 (35) 0.2824	2/70 (16) 0.4340
	Hair Follicle Tumor, Benign	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
	Leiomyosarcoma, Malignant	0/70 (29) 0.4393	0/70 (31) NC	1/70 (32) 0.5246	0/70 (15) NC
	Lipoma, Benign	1/70 (29) 0.8032	2/70 (32) 0.5375	1/70 (32) 0.7781	0/70 (15) 1.0000
	Sarcoma, Undifferentiated, Malignant	0/70 (29) 0.4444	0/70 (31) NC	1/70 (33) 0.5323	0/70 (15) NC
	Schwannoma, Malignant	4/70 (32) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000

male Rats Poly-3 test

Organ Name	Tumor Name	0 mg Vehicle Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Small Intestine, Jejunum	Adenocarcinoma, Malignant	0/70 (29) 0.7315	1/70 (32) 0.5246	0/70 (32) NC	0/70 (15) NC
Spleen	Sarcoma, Stromal, Malignant	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
Stomach, Nonglandular	Papilloma, Squamous Cell, Benign	0/70 (29) 0.7290	1/70 (31) 0.5167	0/70 (32) NC	0/70 (15) NC
Tail	Hair Follicle Tumor, Benign	1/70 (29) 1.0000	0/70 (31) 1.0000	0/70 (32) 1.0000	0/70 (15) 1.0000
Testes	Adenoma, Leydig Cell, Benign	1/70 (29) <0.0001*	5/70 (33) 0.1300	12/70 (38) 0.0033*	15/70 (25) <0.0001*
	Sertoli Cell Tumor, Benign	0/70 (29) 0.1402	0/70 (31) NC	0/70 (32) NC	1/70 (15) 0.3409
Thyroid Gland	Adenoma, C-Cell, Benign	3/70 (30) 0.5772	2/70 (32) 0.8425	3/70 (33) 0.7091	1/70 (15) 0.8161
	Adenoma, Follicular Cell, Benign	2/70 (29) <0.0001*	6/70 (34) 0.1860	36/70 (50) <0.0001*	27/70 (33) <0.0001*
	Carcinoma, C-Cell, Malignant	1/70 (29) 0.5463	0/70 (31) 1.0000	2/70 (33) 0.5491	0/70 (15) 1.0000
	Carcinoma, Follicular Cell, Malignant	1/70 (29) 0.0162	2/70 (32) 0.5375	13/70 (37) 0.0014*	4/70 (17) 0.0549
	Adenoma/ Carcinoma, C-Cell, Benign/Malignant	4/70 (30) 0.6154	2/70 (32) 0.9162	5/70 (34) 0.5818	1/70 (15) 0.8834
	Adenoma/Carcinoma, Follicular Cell, Benign/Malignant	3/70 (30) <0.0001*	8/70 (35) 0.1477	44/70 (53) <0.0001*	29/70 (34) <0.0001*
Urinary Bladder	Papilloma, Transitional Cell, Benign	0/70 (29) 0.1852	1/70 (31) 0.5167	0/70 (32) NC	1/70 (15) 0.3409
Zymbal`S Gland	Carcinoma, Zymbals Gland, Malignant	2/70 (30) 0.9807	1/70 (32) 0.8926	0/70 (32) 1.0000	0/70 (15) 1.0000

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and the pairwise comparisons

		Female Rats Poly-3 test			
Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
Adrenal Glands	Adenoma, Cortical, Benign	8/70 (31) 0.5176	5/70 (30) 0.8822	4/70 (33) 0.9585	7/70 (32) 0.7457
	Pheochromocytoma, Benign	2/70 (27) 0.8718	1/70 (28) 0.8885	3/70 (32) 0.5819	0/70 (28) 1.0000
Bone	Osteosarcoma, Malignant	1/70 (27) 1.0000	0/70 (28) 1.0000	0/70 (30) 1.0000	0/70 (28) 1.0000
Brain	Glioma, Malignant	0/70 (26) 0.3287	1/70 (29) 0.5273	0/70 (30) NC	1/70 (29) 0.5273
	Granular Cell Tumor, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
	Mixed Glioma, Malignant	0/70 (26) 0.3423	1/70 (29) 0.5273	3/70 (33) 0.1678	1/70 (29) 0.5273
	Oligodendroglioma, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Heart	Schwannoma, Endocardial, Benign	0/70 (26) 0.0675	0/70 (28) NC	0/70 (30) NC	2/70 (30) 0.2825
Kidneys	Liposarcoma, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
Liver	Adenoma, Hepatocellular, Benign	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
	Carcinoma, Hepatocellular, Malignant	0/70 (26) 0.0169*	0/70 (28) NC	0/70 (30) NC	3/70 (30) 0.1465
Mammary Gland	Adenocarcinoma, Malignant	18/70 (37) 0.7848	15/70 (37) 0.8252	11/70 (36) 0.9660	14/70 (37) 0.8797
	Adenoma, Benign	4/70 (29) 0.7064	4/70 (30) 0.6663	4/70 (33) 0.7177	3/70 (31) 0.8148
	Adenocarcinoma, Malignant / Adenoma, Benign	22/70 (40) 0.8955	18/70 (39) 0.8440	14/70 (38) 0.9671	15/70 (38) 0.9454
	Fibroadenoma, Benign	26/70 (41) 0.9121	24/70 (42) 0.7903	29/70 (45) 0.5495	18/70 (38) 0.9519
	Hair Follicle Tumor, Benign	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Multicentric Neoplasm	Hemangiosarcoma, Malignant	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
	Lymphoma, Malignant	0/70 (26) 0.0551	1/70 (28) 0.5185	1/70 (31) 0.5439	3/70 (31) 0.1536

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
	Sarcoma, Histiocytic, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Nose	Sarcoma, Undifferentiated, Malignant	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
Ovaries	Adenoma, Tubulostromal, Benign	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
	Sex-Cord/Stromal Tumor, Benign	1/70 (27) 0.7694	0/70 (28) 1.0000	1/70 (31) 0.7877	0/70 (28) 1.0000
	Sex-Cord/Stromal Tumor, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Pancreas	Adenoma, Acinar Cell, Benign	0/70 (26) 0.4724	0/70 (28) NC	3/70 (32) 0.1607	0/70 (28) NC
	Adenoma, Islet Cell, Benign	0/70 (26) 0.4724	0/70 (28) NC	3/70 (32) 0.1607	0/70 (28) NC
	Carcinoma, Islet Cell, Malignant	1/70 (27) 0.4457	0/70 (28) 1.0000	0/70 (30) 1.0000	1/70 (29) 0.7721
Parathyroid Glands	Adenoma, Benign	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
Pituitary Gland	Adenoma, Pars Distalis, Benign	53/70 (59) 0.9488	53/70 (59) 0.6190	49/70 (57) 0.8220	41/70 (51) 0.9529
	Carcinoma, Pars Distalis, Malignant	6/70 (30) 0.9581	6/70 (31) 0.6498	3/70 (32) 0.9403	2/70 (29) 0.9707
	Adenoma / Carcinoma, Pars Distalis, Benign/Malignant	59/70 (63) 0.9924	59/70 (63) 0.6413	52/70 (58) 0.8703	43/70 (53) 0.9911
Skin	Carcinoma, Squamous Cell, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Skin, Subcutis	Basal Cell Tumor, Benign	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Carcinoma, Sebaceous Cell, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
	Fibroma, Benign	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Fibrosarcoma, Malignant	0/70 (26) 0.6443	1/70 (29) 0.5273	1/70 (31) 0.5439	0/70 (28) NC
	Osteosarcoma, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Sarcoma, Undifferentiated, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC

Female Rats Poly-3 test

Organ Name	Tumor Name	0 mg Cont (N=70) P - Trend	0.5 mg Low (N=70) P - C vs. L	1.5 mg Med (N=70) P - C vs. M	5/3 mg High (N=70) P - C vs. H
	Schwannoma, Malignant	1/70 (27) 1.0000	0/70 (28) 1.0000	0/70 (30) 1.0000	0/70 (28) 1.0000
Stomach, Nonglandular	Carcinoma, Squamous Cell, Malignant	0/70 (26) 0.7679	1/70 (28) 0.5185	0/70 (30) NC	0/70 (28) NC
Thymus	Thymoma, Benign	1/70 (27) 1.0000	0/70 (28) 1.0000	0/70 (30) 1.0000	0/70 (28) 1.0000
	Thymoma, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
Thyroid Gland	Adenoma, C-Cell, Benign	1/70 (27) 0.1340	4/70 (30) 0.2108	4/70 (32) 0.2342	5/70 (31) 0.1315
	Adenoma, Follicular Cell, Benign	0/70 (26) <0.0001*	2/70 (29) 0.2734	12/70 (37) 0.0007*	28/70 (43) <0.0001*
	Carcinoma, Follicular Cell, Malignant	0/70 (26) 0.0010*	0/70 (28) NC	2/70 (32) 0.3001	6/70 (32) 0.0224*
	Adenoma/Carcinoma, Follicular Cell, Benign/Malignant	0/70 (26) <0.0001*	2/70 (29) 0.2734	13/70 (37) 0.0003*	32/70 (45) <0.0001*
Uterus with Cervix	Granular Cell Tumor, Benign	2/70 (28) 0.0018*	1/70 (29) 0.8880	6/70 (34) 0.2003	10/70 (34) 0.0269
	Granular Cell Tumor, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Polyp, Endometrial Stromal, Benign	6/70 (30) 0.9525	6/70 (31) 0.6498	4/70 (32) 0.8745	2/70 (29) 0.9707
	Polyp, Stromal, Benign	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Sarcoma, Endometrial Stromal, Malignant	1/70 (27) 0.7694	0/70 (28) 1.0000	1/70 (31) 0.7877	0/70 (28) 1.0000
	Sarcoma, Stromal, Malignant	0/70 (26) 0.2145	0/70 (28) NC	2/70 (32) 0.3001	1/70 (29) 0.5273
Vagina	Granular Cell Tumor, Benign	3/70 (28) 0.0896	1/70 (28) 0.9443	0/70 (30) 1.0000	5/70 (31) 0.4133
	Granular Cell Tumor, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC
	Polyp, Endometrial Stromal, Benign	0/70 (26) 0.2566	0/70 (28) NC	0/70 (30) NC	1/70 (29) 0.5273
	Sarcoma, Stromal, Malignant	0/70 (26) 0.5221	0/70 (28) NC	1/70 (31) 0.5439	0/70 (28) NC

Figure 1A: Kaplan-Meier Survival Curves for Male Rats

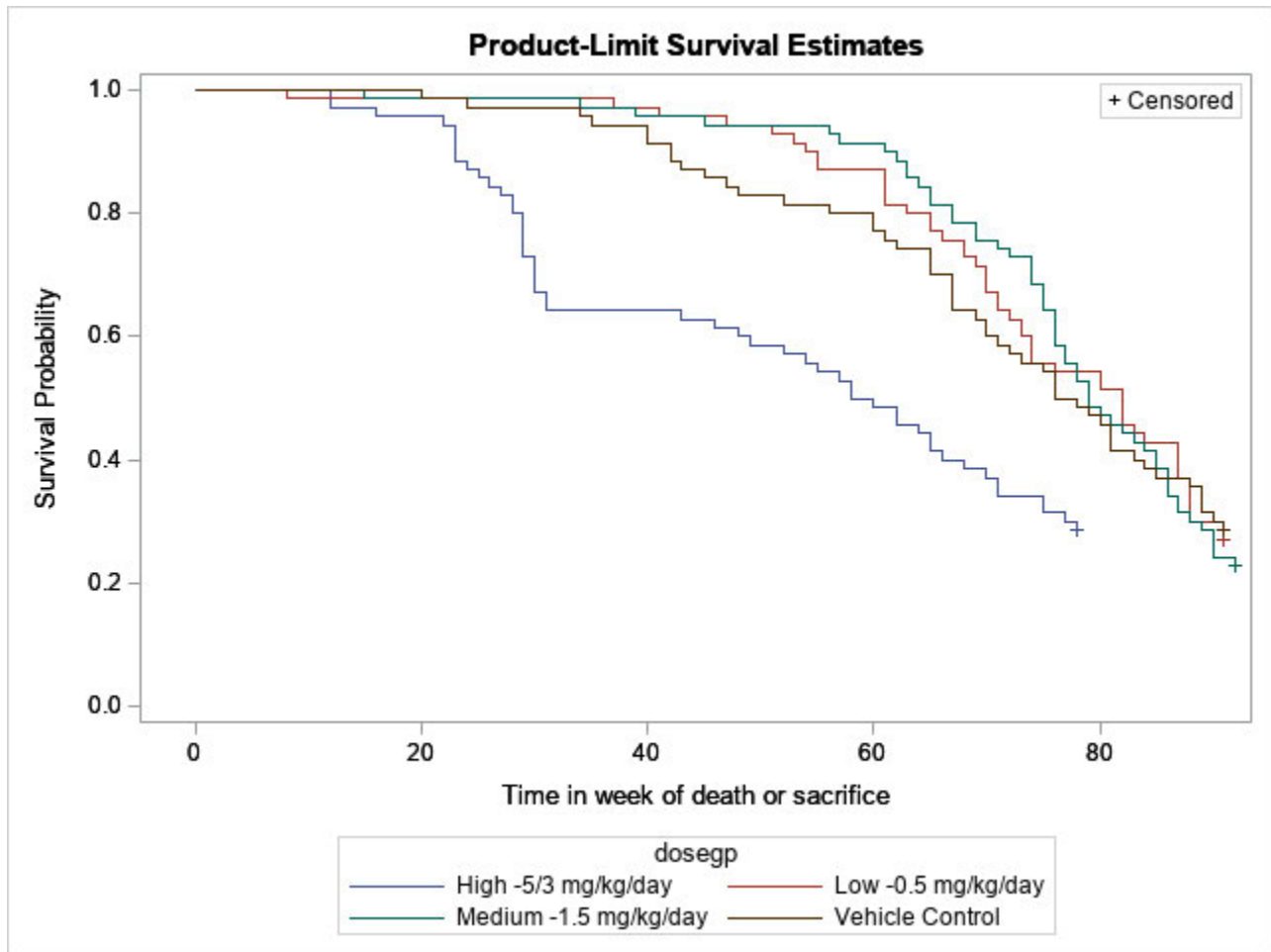


Figure 1B: Kaplan-Meier Survival Curves for Female Rats

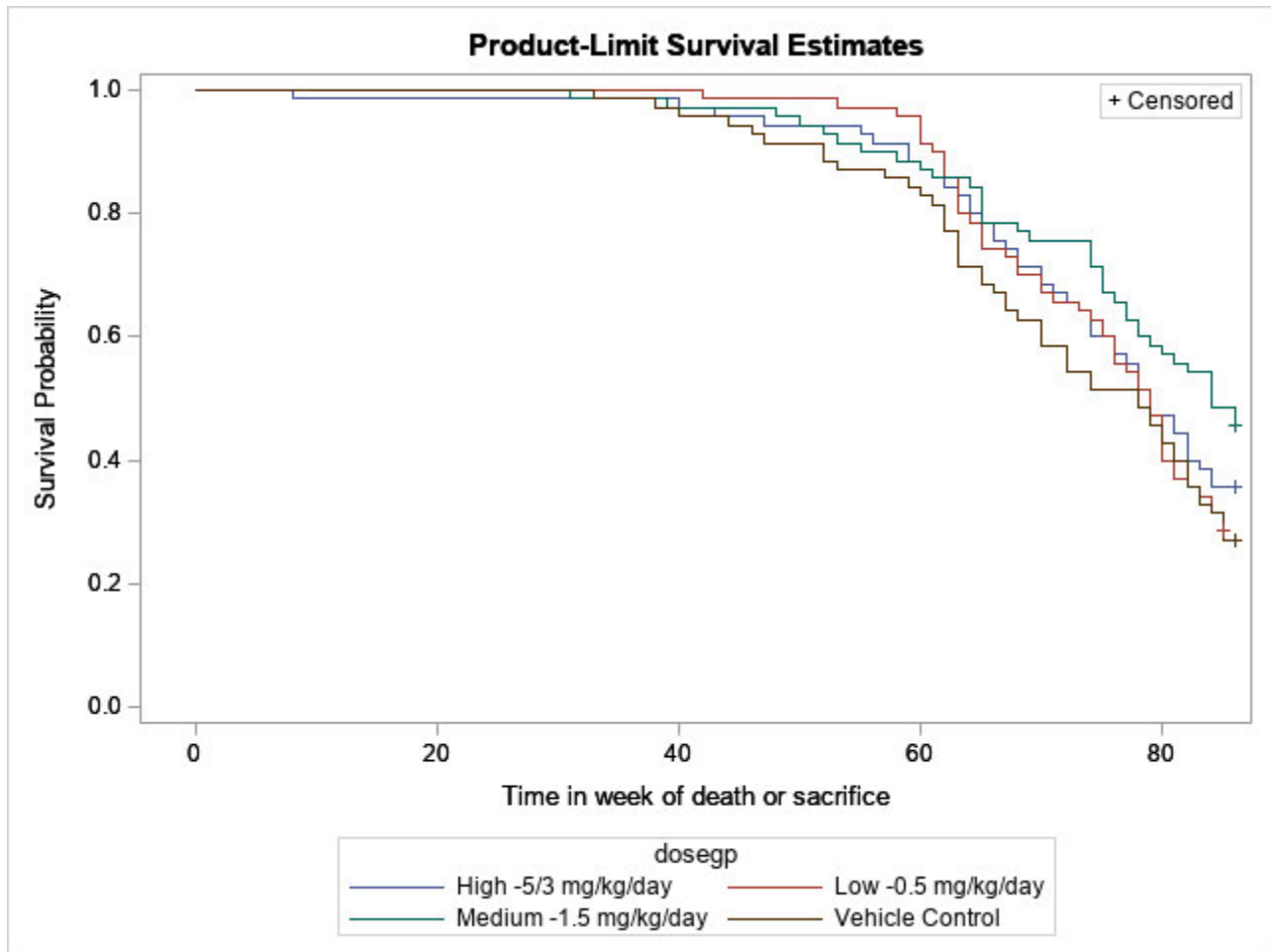


Table 1A: Intercurrent Mortality Rate
Male Mice

Week	0 mg/kg/day Vehicle Control		0.5 mg/kg/day Low		1.5 mg/kg/day Medium		5 mg/kg/day High		75 mg/kg/day Positive	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	1	4.00	1	4.00	.	.
14 - 27	1	4.00	1	4.00	.	.	1	8.00	2	13.33
Ter. Sac.	24	96.00	24	96.00	24	96.00	23	92.00	13	86.67
Total	25	100.00	25	100.00	25	100.00	25	100.00	15	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 1B: Intercurrent Mortality Rate
Female Mice

Week	0 mg/kg/day Vehicle Control		1.5 mg/kg/day Low		5 mg/kg/day Medium		15 mg/kg/day High		75 mg/kg/day Positive	
	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	1	4.00	1	4.00	.	.	1	4.00	.	.
14 - 26	1	8.00	.	.	.	.	1	8.00	3	20.00
Ter. Sac.	23	92.00	24	96.00	25	100.00	23	92.00	12	80.00
Total	25	100.00	25	100.00	25	100.00	25	100.00	20	100.00

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded

Table 5A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	P-value for Vehicle Control, Low, Med, high	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive Control
Dose-Response (Likelihood Ratio)	0.4688	0.9885	0.9885	0.5521	0.3085
Homogeneity (Log-Rank)	0.8941	0.9885	0.9885	0.5557	0.2986

Table 5B: Intercurrent Mortality Comparison for
Female Mice

Test Statistics	P-value for Vehicle Control Low, Med, high	P-value for Vehicle Control vs Low	P-value for Vehicle Control vs Med	P-value for Vehicle Control vs High	P-value for Vehicle Control vs Positive Control
Dose-Response (Likelihood Ratio)	0.7386	0.5678	0.0935	0.9834	0.3174
Homogeneity (Log-Rank)	0.5246	0.5717	0.1531	0.9834	0.3077

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and the Pairwise Comparisons
Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Veh Cont (N=25) P - Trend	0.5 mg Low (N=25) P - VC vs. L	1.5 mg Med(N=25) P - VC vs. M	5 mg High (N=25) P - VC vs. H	75 mg Posi (N=15) P - VC vs. PC
harderian glands	Adenocarcinoma, Malignant	0/25 (24) 0.0593	0/25 (25) NC	0/25 (24) NC	2/25 (24) 0.2447	0/15 (14) NC
	Adenoma, Benign	2/25 (24) 0.9823	2/25 (25) 0.7110	0/25 (24) 1.0000	0/25 (24) 1.0000	2/15 (14) 0.4722
lung	Adenoma, Bronchiolar Alveolar, Benign	1/25 (24) 0.2385	3/25 (25) 0.3202	1/25 (24) 0.7553	3/25 (24) 0.3043	1/15 (14) 0.6074
multicentric neoplasm	Hemangiosarcoma, Malignant	0/25 (24) 0.1493	3/25 (25) 0.1248	1/25 (24) 0.5000	3/25 (25) 0.1248	1/15 (14) 0.3684
	Lymphoma, Malignant	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	3/15 (14) 0.0431*
skin	Papilloma, Benign	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	5/15 (14) 0.0040*
stomach	Carcinoma, Squamous Cell, Malignant	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	2/15 (15) 0.1417
	Papilloma, Benign	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (24) NC	12/15 (15) <0.0001*

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and the Pairwise Comparisons
Female Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg Veh Cont (N=25) P - Trend	15 mg Low (N=25) P - VC vs. L	50 mg Med(N=25) P - VC vs. M	150 mg High (N=25) P - VC vs. H	75 mg Posi (N=15) P - VC vs. PC
Cavity, Oral	Schwannoma, Malignant	0/25 (23) 0.2500	0/25 (24) NC	0/25 (25) NC	1/25 (24) 0.5106	0/15 (14) NC
Harderian Glands	Adenocarcinoma, Malignant	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (14) 0.3784
	Adenoma, Benign	0/25 (23) 0.2760	0/25 (24) NC	3/25 (25) 0.1330	1/25 (24) 0.5106	3/15 (14) 0.0468*
Liver	Adenoma, Hepatocellular, Benign	0/25 (23) 0.2500	0/25 (24) NC	0/25 (25) NC	1/25 (24) 0.5106	0/15 (14) NC
Lung	Adenoma, Bronchiolar Alveolar, Benign	0/25 (23) 0.7516	2/25 (24) 0.2553	2/25 (25) 0.2660	0/25 (24) NC	2/15 (14) 0.1366
	Carcinoma, Bronchiolar Alveolar, Maligna	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	2/15 (14) 0.1366
Multicentric Neoplasm	Hemangioma, Benign	0/25 (23) 0.7604	1/25 (24) 0.5106	0/25 (25) NC	0/25 (24) NC	0/15 (14) NC
	Hemangiosarcoma, Malignant	3/25 (24) 0.4427	0/25 (24) 1.0000	2/25 (25) 0.8384	2/25 (25) 0.8384	1/15 (14) 0.8560
	Lymphoma, Malignant	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	3/15 (15) 0.0539
Skin	Carcinoma, Basosquamous Cell, Malignant	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (14) 0.3784
	Carcinoma, Neuroepithelial, Malignant	0/25 (23) 0.7629	1/25 (25) 0.5208	0/25 (25) NC	0/25 (24) NC	0/15 (14) NC
	Papilloma, Benign	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	6/15 (15) 0.0018*
Stomach	Carcinoma, Adenosquamous, Malignant	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (14) 0.3784
	Papilloma, Benign	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	13/15 (15) <0.0001*
Thymus	Adenoma, Benign	1/25 (23) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/15 (14) 1.0000
	Thymoma, Malignant	1/25 (23) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/15 (14) 1.0000
Urethra	Papilloma, Transitional Cell, Benign	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (14) 0.3784
Uterus with Cervix	Adenoma, Benign	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (15) 0.3947

Organ Name	Tumor Name	0 mg Veh Cont (N=25) P - Trend	15 mg Low (N=25) P - VC vs. L	50 mg Med(N=25) P - VC vs. M	150 mg High (N=25) P - VC vs. H	75 mg Posi (N=15) P - VC vs. PC
	Carcinoma, Adenosquamous, Malignant	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	1/15 (14) 0.3784
	Polyp, Endometrial Stromal, Benign	0/25 (23) NC	0/25 (24) NC	0/25 (25) NC	0/25 (24) NC	5/15 (15) 0.0060*

Figure 2A: Kaplan-Meier Survival Curves for Male Mice

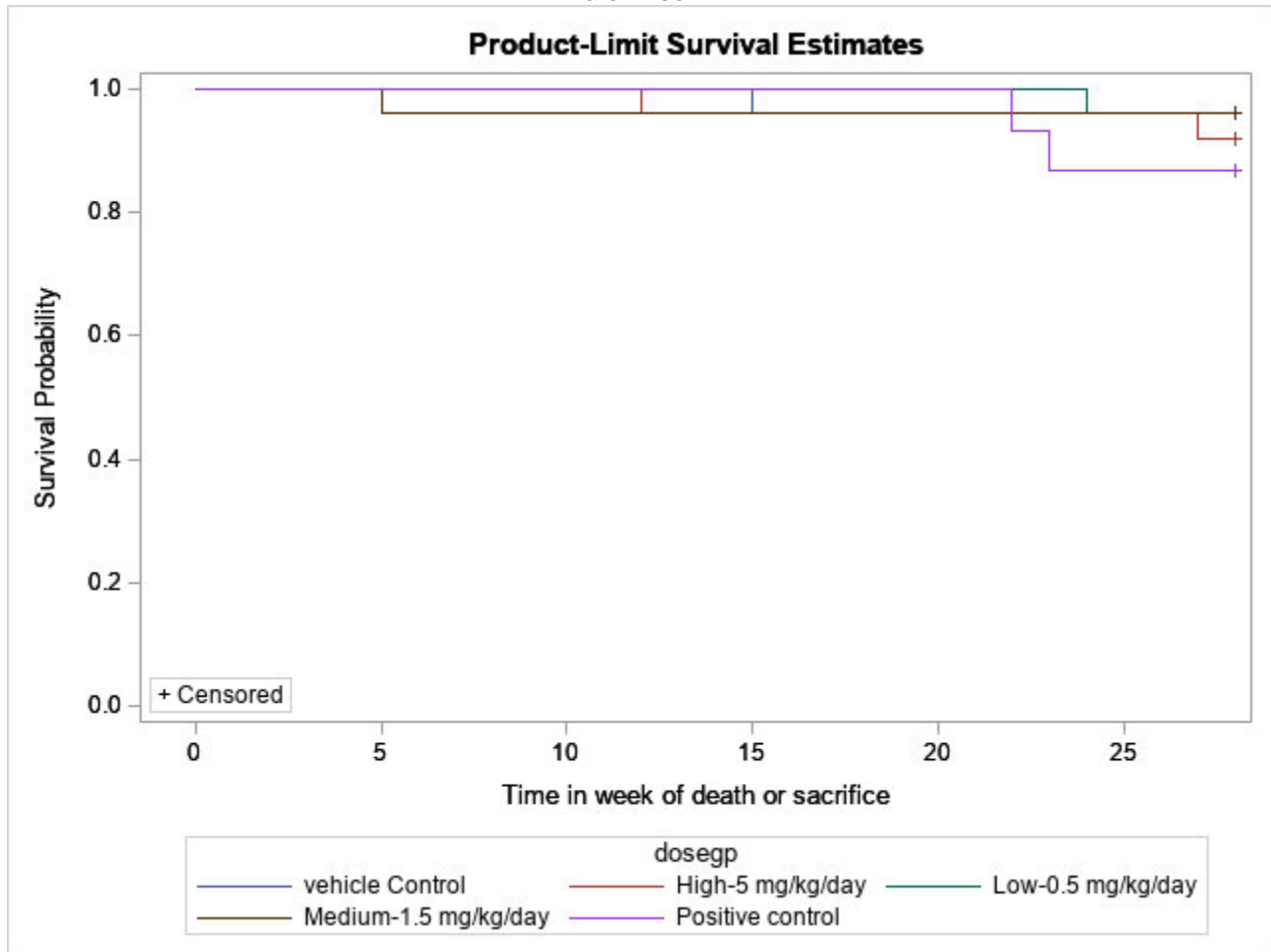
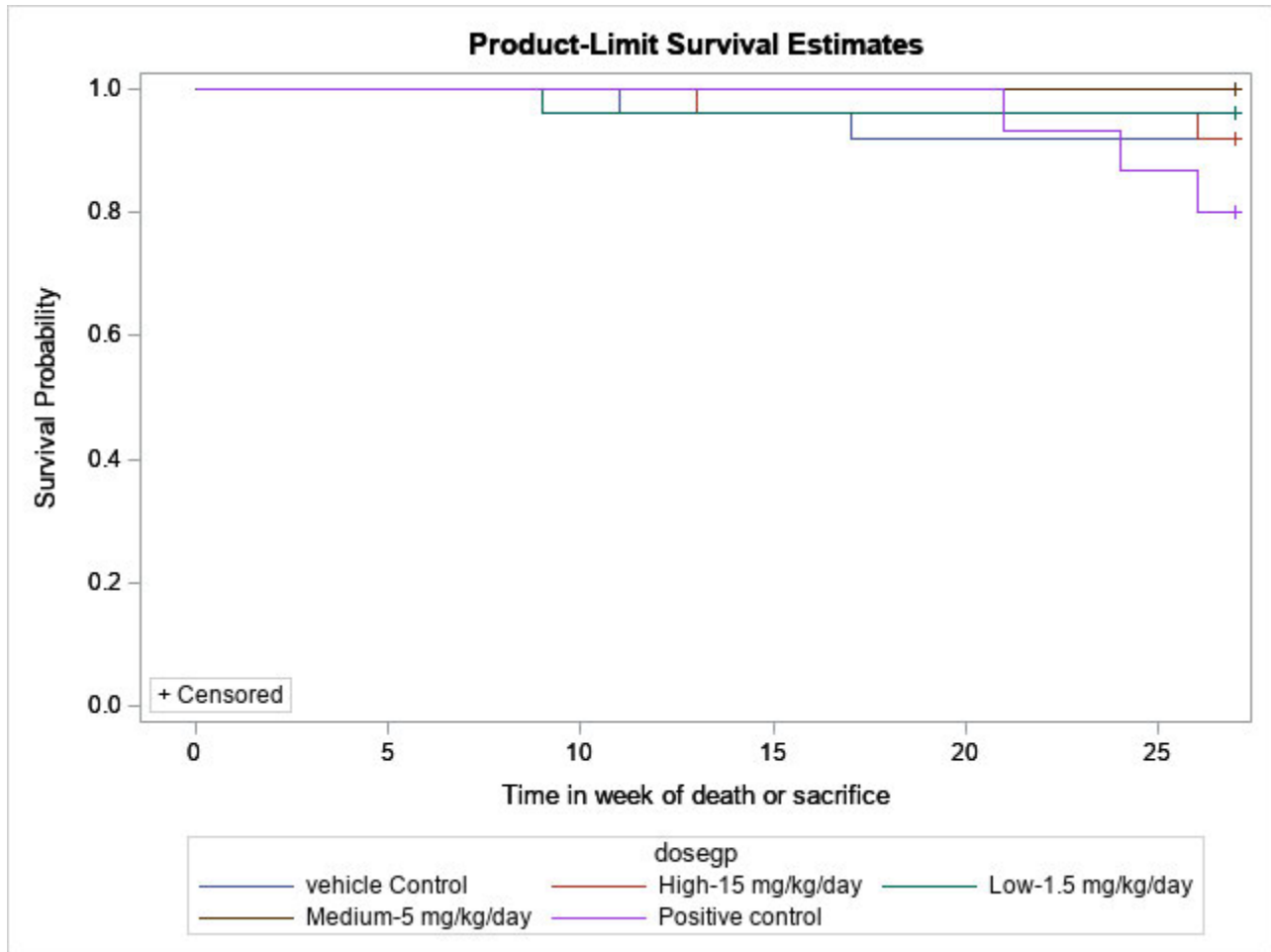


Figure 2B: Kaplan-Meier Survival Curves for Female Mice



6. References:

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/s/

MALICK MBODJ
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Concur with review.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY CONSULT ASSESSMENT AND EVALUATION

Application Number*: NDA 215888 (IND 111675)

Sponsor: Mycovia Pharmaceuticals, Inc.

Product: VIVOJA (oteseconazole), capsule,
150 mg

Therapeutic area: Antifungal Agents- Systemic

Review Division: DAI

Reviewer: Lori Kotch, PhD, DABT

Division Director: Mukesh Summan, PhD

OID/DAI Contact: Gregory DiBernardo, 301-796-4063

Purpose of Review: Other

Consult Review

Requested Completion Date: October 1, 2021

Executive Summary (Clinical Relevance)

Consult Questions/ Responses

The PharmTox team in DAI request DPT-ORPUM input for the following questions related to cataract findings in PPND studies:

- 1) These findings will be described in the prescribing information. Based on the presence of the cataracts, which appear to develop in multiple rat strains after PND 21, do you recommend additional studies to evaluate the risk of prenatal or neonatal exposure to oteseconazole to the offspring of patients? If so, what study design or additional ocular findings merit further evaluation (e.g., vision and visual acuity testing, etc.)?

DPT-ORPUM Response: The multiple reproductive toxicity studies provided are adequate to characterize risk; I do not recommend additional studies. I am not aware of an accepted method to assess vision/visual acuity in animal models. However, given the toxicity (cataracts) one can presume effects to vision, the extent to which would be determined by severity of toxicity.

- 2) Have you previously observed similar ocular findings in pre- and post- natal, nonclinical animal studies, and if so, can you comment on the reversibility of these findings and what actions were taken based on the findings?

DPT-ORPUM Response: I have not observed cataracts in previous PPND studies in this Division. Cataracts are generally not reversible.

Please note that cataracts would not be detected in an EFD study. Eyelids are closed at/around time of birth (i.e. no clinical observations) and sectioning methods (i.e. Bouins fixation, razor sectioning) preclude cataract determination. Skeletal processing methods remove all soft tissues and examination of ocular tissues is not possible in fetuses assigned to skeletal exam.

- 3) Based on these findings and your prior observations, would there be heightened potential for the described findings to occur in humans, particularly when considering the exposure at the NOAEL (1 mg/kg associated with an AUC of 39,360 ng*hr/mL) (in Pre- Post-natal study # 12344001) was about 0.5 times the clinical exposure (as well as the drug's long t_{1/2})?

DPT-ORPUM Response: Treatment-related cataracts were produced in multiple reproductive toxicity studies, using multiple strains. Based on risk

estimate (0.5 times clinical exposure at NOAEL), it is reasonable to be concerned that such findings may occur in patients at clinical dose. The long half-life of the drug further elevates concern.

Relevant Background Provided by Requesting Division:

On May 27, 2021, a type 1, NME for oteseconazole was submitted under NDA 215888 for FDA review. This product has QIDP and Fast Track designations and will be reviewed as a Priority NDA under the "Program." We currently do not plan to hold an Advisory Committee meeting for this NDA.

5/27/21 EDR Location: [\\CDSESUB1\evsprod\NDA215888\0001](#)

In Pre- Post-natal study 12344001, oral administration of oteseconazole to pregnant SD rats at 0, 1, 3 and 7.5 mg/kg/day once daily from Gestation Day 6 through Lactation Day 20 resulted in eye opacities at doses as low as 3 mg/kg. Opacities were observed (during clinical evaluations) as early as Day 21 (but not on Day 17). Some animals only developed cataracts/opacities beginning Day 49 or 56 or 84. The development of these opacities/cataracts was confirmed in three subsequent studies (#1234002, 1234003 and 1234004), where only the 7.5 mg/kg dose was used and ocular examinations were conducted by a board-certified veterinary ophthalmologist in both preweaned and weaned rat pups (generally PND 17–22 and PND 30–36) using an indirect ophthalmoscope and slit lamp biomicroscope. Assuming clinical exposure of 85,000 ng·hr/mL, the exposure at the NOAEL (1 mg/kg associated with an AUC of 39,360 ng·hr/mL) was about 0.5 times the clinical exposure for patients being treated for acute vulvovaginal candidiasis.

Table 1: Eye findings from Pre- Post-natal study 12344001

Animal ID	Study Phase	Sex	Group	Clinical signs	Finding noted on PND	Subgroup
4040-12	Main	F	4	exophthalmos left eye opacity left eye	21 and 28-108 49-108	Selected for F ₁ Generation; Euthanized on PND 108
4090-03	Main	F	4	exophthalmos left eye	21	Euthanized on PND 21
4114-08	Main	F	4	exophthalmos left eye opacity left eye partial closure left eye	21 84 49-91	Selected for F ₁ Generation; Euthanized on PND 95
4114-09	Main	F	4	exophthalmos right eye	21	Euthanized on PND 21
4075-10	Main	M	4	exophthalmos left eye	21	Euthanized on PND 21
4090-01	Main	M	4	exophthalmos right eye opacity right eye	21 and 25-91 56-91	Selected for F ₁ Generation; ; Euthanized on PND 95
4080-16	TK	F	4	partial closure right eye red discharge right eye enophthalmos right eye	21 21, 42, and 49 PND 35	Selected for F ₁ Generation; Euthanized on PND 120
4096-11	TK	F	4	exophthalmos left eye	PND 21	Euthanized on PND 21
4115-08	TK	F	3	Bilateral opacity	PND 21	Euthanized on PND 21

M = Males, F = Females, PND = Postnatal Day

In pre-postnatal study #1234004, 7.5 mg/kg oteseconazole was administered to two strains of rats, (Sprague Dawley (SD) and Wistar Han (HAN)). A high incidence of lens opacities/cataracts was observed in the 7.5 mg/kg/day groups during the preweaning evaluation on PND 17–22, (11 and 32 pups for SD and HAN, respectively) which were seen for only a single female in the

SD control group and not seen in the HAN control group. The higher incidence of lens cataract was also observed at PND 30–36 (30 and 27 animals for SD and HAN, respectively) when compared to the respective control groups (7 and 0 for SD and HAN, respectively). No cataract/opacity was reported during the embryo-fetal development study of oteseconazole. Half of the fetuses were processed for skeletal examination while half were fixed in Bouin's solution and examined for soft tissue defects using the Wilson razor-blade sectioning technique.

We seek your input on the following questions:

- 4) These findings will be described in the prescribing information. Based on the presence of the cataracts, which appear to develop in multiple rat strains after PND 21, do you recommend additional studies to evaluate the risk of prenatal or neonatal exposure to oteseconazole to the offspring of patients? If so, what study design or additional ocular findings merit further evaluation (e.g., vision and visual acuity testing, etc.)?
- 5) Have you previously observed similar ocular findings in pre- and post- natal, nonclinical animal studies, and if so, can you comment on the reversibility of these findings and what actions were taken based on the findings?
- 6) Based on these findings and your prior observations, would there be heightened potential for the described findings to occur in humans, particularly when considering the exposure at the NOAEL (1 mg/kg associated with an AUC of 39,360 ng*hr/mL) (in Pre- Post-natal study # 12344001) was about 0.5 times the clinical exposure (as well as the drug's long $t_{1/2}$)?

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